INDEX NUMBER DOES NOT CIRCULATE

American Academy of Allergy, Twelfth Annual Meeting, Chase-Park Plaza Hotels, St. Louis, Missouri, February 6, 7, 8, 1956

UNIVERSITY OF MICHIGAN
NOV 29 1956
MEDICAL LIBRARY

The Journal of Allergy

Official Organ of AMERICAN ACADEMY OF ALLERGY

Including
ALLERGY ABSTRACTS

CONTENTS FOR NOVEMBER, 1955

Original Articles

"Stresses" and Hypersensitivity. Carlos Benaim, M.D., Samuel M. Feinberg, M.D., and Ludwig A. Sternberger, M.D., Chicago, Ill. ---------- 481

Studies in Pulmonary Ventilatory Function. I. Vital Capacity, First One-Second Capacity, and Forced Respiratory Curves in Patients With Asthma: Comparative Evaluation of Methods. Jean Roy, M.D., H. Beecher Chapin, M.D., and Jean Favre, M.D., New York, N. Y. ---------- 490

Effects of the Histamine Liberator 48/80 In Histamine-Sensitive Mice. L. S. Kind, Ph.D., Charleston, S. C. ---------- 507

(*Contents Continued on Page 2*)

Vol. 26, No. 6 NOVEMBER, 1955

PUBLISHED BI-MONTHLY BY THE C. V. MOSBY CO., ST. LOUIS 3, MO.

as an antihistaminic agent

Pyribenzamine® *is unsurpassed*

in hay fever . . .

in allergic rhinitis

in urticaria

in serum sickness

in angioneurotic edema

in drug reaction

for maximum relief

with minimal side effects

Pyribenzamine® hydrochloride
(tripelennamine hydrochloride CIBA)

C I B A Summit, N. J.

MEDICAL HORIZONS TV Monday P.M. *Sponsored by* CIBA ABC-TV

2/2021M

The Journal of Allergy

VOL. 26 NOVEMBER, 1955 No. 6

Original Articles

"STRESSES" AND HYPERSENSITIVITY

EFFECT OF ADRENALECTOMY IN THE GUINEA PIG ON ASTHMA FROM ANTIGEN AND HISTAMINE AEROSOLS AND ON ITS INHIBITION BY A NONSPECIFIC SUBSTANCE, SODIUM NUCLEATE

CARLOS BENAIM, M.D.,* SAMUEL M. FEINBERG, M.D., AND LUDWIG A. STERNBERGER, M.D., CHICAGO, ILL.

IT IS a common clinical observation that acute infections, with and without fever, produce remissions of varying duration in persistent allergic manifestations. The relief from asthma and other allergic conditions is frequently greater than that obtained by long-term specific desensitization. Such remissions may be initiated by a number of other circumstances, commonly classed as "stresses," such as major surgery, traumatic shock, nervous shock, icterus, vomiting, diarrhea, or pregnancy. It is not known whether all these conditions operate by the same mechanism.

In 1931 we reported[1] on the results of the treatment of intractable asthma with fever produced by diathermy. Although relief was obtained for short periods of time in most patients, we realized that fever therapy alone was not a satisfactory answer to our problem. We were aware also that, although over decades various forms of nonspecific therapy had been advocated in the treatment of allergy, their efficacy was debatable and their basis was usually empiric. We decided several years ago, therefore, that a plan of systematic research, largely in the laboratory and on experimental animals, would be required to learn about mechanisms involved in such remissions.

Our efforts to inhibit anaphylactic shock in the guinea pig by pretreatment with "stress" procedures, such as abscess or fever, failed. When cortisone and

From the Allergy Research Laboratory, Northwestern University Medical School, Chicago, Ill.

This investigation was supported by Research Grant No. G-3848 from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

Presented at the Eleventh Annual Meeting of the American Academy of Allergy, New York, N. Y., Feb. 7 to 9, 1955.

Received for publication March 7, 1955.

*Fellow in Medicine (Allergy), Northwestern University Medical School, Chicago, Ill. (Sponsored by the Junta de Beneficencia Publica del Distrito Federal, Caracas, Venezuela.)

ACTH[2] also failed to protect the guinea pig against anaphylactic death, in spite of significant relief obtained with these hormones in human asthma, we realized that anaphylactic death in the guinea pig and asthma or other allergy in man are not comparable. Either of two possible major differences could explain this phenomenon: (1) man and guinea pig may be qualitatively different in their response or (2) the responses we are comparing are quantitatively different. When asthma or hay fever in man is relieved by an acute infection, one does not prevent imminent death from these allergies. Indeed, there is ample evidence that an acute infection or any other stress or any other medication fails to prevent acute, severe allergic responses in man, such as anaphylactic reaction from penicillin or horse serum. Therefore, a method of response in the guinea pig was sought which would more closely resemble clinical conditions in man. The method finally adopted was the production of asthma in the passively sensitized guinea pig by an aerosol of crystallized egg albumin. With this method, it was found[3] that cortisone and ACTH produced a significant inhibiting effect. It was found, further, that such asthma in the guinea pig could be inhibited or modified by pretreatment procedures,[4] such as the production of a sterile abscess, the injection of human serum, yeast suspension, sodium nucleate, adenosine triphosphate, and adenosine diphosphate.

The question arising next was: How is this inhibition mediated? In line with current concepts of the effect of "stresses" on the pituitary-adrenal axis, it was obvious that the first question that needed to be considered was the role of the adrenals. This could be examined by observing the effect of these inhibiting procedures on adrenal function, such as ascorbic acid content, leukocyte response, ACTH assay, blood or urinary corticoids, or a number of other effects. We realized, however, that no matter what the results of such findings, it would not prove that these functional changes have anything to do with the mechanism of inhibition of asthma by nonspecific procedures. On the other hand, the interpretation of the effect of these inhibiting procedures on adrenalectomized animals could leave very little room for doubt.

PROCEDURES AND RESULTS

Adrenalectomy.—Bilateral adrenalectomy in the guinea pig is a formidable procedure because of anatomic difficulties and because of difficulty of survival without adrenals. Many animals were lost before surgical technique was mastered and before the most appropriate ancillary measures were adopted. In the course of these trials and experiments, more than 200 animals were subjected to bilateral adrenalectomy. The right adrenal is closely attached to the inferior vena cava and to the liver and, in removing this gland, serious hemorrhage is difficult to avoid. We also believe that we lost animals in our early experiments because we used too large doses of cortisone, DOCA, or adrenocortical extract. Our attempts to perform experiments a long time after adrenalectomy also resulted in deaths in most animals, thus delaying our final experimental results. These experiences are at variance with those of

some other workers,[5, 6] who claimed that adrenalectomized guinea pigs survive for a long time when given either DOCA or supplementary salt solution. Even with our final procedure, the mortality rate was still high.

The procedure finally adopted was as follows: The right adrenal was removed first and the left one was removed five to eighteen days later. One milligram of DOCA, intramuscularly, was given forty-eight and twenty-four hours prior to removal of the second adrenal. A few minutes before the second operation, 2 mg. of DOCA was administered. The day after the operation, and thirty hours before challenge, 1 mg. of DOCA was administered. The animal was passively sensitized with guinea pig antiegg albumin serum, as a rule, several hours before the second adrenalectomy. It was exposed forty-eight hours later to the aerosol of crystalline egg albumin. Sodium nucleate, shown in previous experiments to be a substance which inhibits or modifies the asthma response, was injected intramuscularly twenty-one and four hours prior to exposure to the antigen aerosol.

Standardization of Serum.—Serum was obtained from a number of guinea pigs which had been sensitized by two simultaneous intramuscular injections, each containing 10 mg. of crystallized egg albumin in Freund's complete adjuvants.[7] The guinea pigs were bled by cardiac puncture seven weeks later, and weekly subsequently. The sera were pooled and, after addition of Merthiolate to 1:10,000, sterilized by Seitz filtration. Groups of animals were given an intravenous injection of antiserum in varying amounts. Forty-eight hours later the animals were placed in an aerosol obtained from a 0.2 per cent solution of crystallized egg albumin at a pressure of 6 pounds. The end point

TABLE I. STANDARDIZATION OF SERUM 1235 (97μg Ab N./ml.)

MILLILITERS PER KILOGRAM ANTISERUM INTRAVENOUSLY	0.5		0.25		0.125		0.0625		0.0312	
Individual end points	1'25"	55"	55"	45"	1'35"	1'10"	10'	3'	10'	5'30"
	1'20"	55"	60"	50"	1'30"	1'	6'	8'	10'	10'
	1'05"	40"	35"	1'20"	1'15"	1'				
					45"	1'30"				
					1'	1'				
					2'	1'				
					1'	1'45"				
Mean	(6 animals) 1'03"		(6 animals) 56"		(14 animals) 1'15"		(4 animals) 6'45"		(4 animals) 8'52"	

was considered to be coughing or gasping followed by dyspnea. The amount of antiserum selected for future experiments was the smallest quantity which gave an end point close to two minutes. With Pool 1235, for example, this was 0.125 ml. per kilogram, while with Pool 1102 this was 0.25 ml. per kilogram. Table I shows an example of one of these experiments, indicating the time of the individual responses and their mean.

Standardization of Histamine Response.—An aerosol of histamine was employed to determine the sensitivity of the bronchi of animals to be used for

antigen experiments, as well as to compare the effect of the various procedures with that obtained by an antigen aerosol. Here the desired end point was also under two minutes. An occasional animal was not very sensitive to histamine; such an animal was discarded. Table II represents such a standardization. It is evident that, for the conditions of our experiments, the 0.2 mg. per milliliter was the weakest solution producing the desired range of response. A much stronger aerosol might mask a moderate inhibiting effect. A weaker aerosol would make some of the control animals insufficiently reactive so that an inhibiting effect in the experimental group could not be easily ascertained.

TABLE II. STANDARDIZATION OF HISTAMINE AEROSOL IN GUINEA PIGS

HISTAMINE CONCENTRATION	0.1 MG. PER MILLILITER	0.2 MG. PER MILLILITER	0.25 MG. PER MILLILITER	0.3 MG. PER MILLILITER
Individual end points	7'15" 5' 1' 40" 10' 4' 50" 1'20"	2'10" 1'20" 1'10" 1' 50" 1' 1'05" 45" 1'05" 1'25" 1'25" 1'45" 1'10" 25" 1'35" 55" 40" 45" 1'10" 40" 1'05" 1'20" 1'10" 45" 1'20" 1'10" 50" 50" 1'50" 1'45" 1'05" 50" 1'30" 1'15" 1'20"	40" 35" 30" 45" 1'05" 30" 40" 45" 40" 35" 45" 50" 45" 40" 1' 1' 1'20" 45" 35" 45" 1'10" 1'30" 30"	40" 45" 25" 30" 45" 30" 30" 35"
Mean	3'45"	1'09"	48"	35"
Range	40" to 10' (8 animals)	25" to 2'10" (35 animals)	30" to 1'30" (23 animals)	25" to 45" (8 animals)

Effect of Sham Adrenalectomy on Response to Histamine Aerosol.—Two complete bilateral operations were done, five days apart, traumatizing tissue but without removing the adrenals. As seen in Tables III and IV, such a major operation did not have any appreciable inhibiting effect on the asthma produced by an antigen or histamine aerosol when the animals were challenged one to seven days after the operation.

Effect of Injection of Sodium Nucleate Intramuscularly on Asthma From Antigen and Histamine Aerosols.—Injection of sodium nucleate was selected as the nonspecific procedure to be used in the present experiments. Although

TABLE III. EFFECT OF SHAM ADRENALECTOMY ON RESPONSE TO ANTIGEN AEROSOL

TIME OF CHALLENGE AFTER SURGERY	2 DAYS	3 DAYS	5 DAYS	7 DAYS
Individual end points	2'25" 2' 10' 1'55" 1'15" 1'30" 2'15" 1'15" 60" 1'15" 1'30" 35"	1'40" 1'40" 4'20"	2' 1'45" 4'40"	2'05" 1'40" 1'05" 2'
Mean	(12 animals) 2'14"	(3 animals) 2'33"	(3 animals) 2'48"	(4 animals) 1'42"

TABLE IV. EFFECT OF SHAM ADRENALECTOMY ON RESPONSE OF HISTAMINE AEROSOL

	DAY 0	1	2	3	5	7
	PRIOR TO SURGERY	FIRST SHAM ADRENAL-ECTOMY	1 DAY AFTER	2 DAYS AFTER	3 DAYS AFTER	SECOND SHAM ADRENAL-ECTOMY	7 DAYS AFTER
Individual end points	1'40" 40"		2'45" 55"	2'40" 50"	2'30" 1'20"		1'15" 2'15"
	45" 1'10"		45" 25"	45" 55"	60" 1'05"		1'30" 45"
	40" 1'05"		1'45" 1'30"	2' 55"	2' 50"		60" 1'15"
	1'10" 20"		45" 35"	55" 20"	1'10" 30"		1'30" 35"
	35" 35"		40" 45"	45" 30"	50" 25"		
	60" 25"		1'20" 25"	1'40" 30"	1'20" 40"		
	25" 1'15"		30" 45"	35" 1'30"	1'20" 1'50"		
	45" 35"		45" 30"	60" 30"	40" 20"		
	(16 animals)		(16 animals)	(16 animals)	(16 animals)		(8 animals)
Mean	49"		57"	1'01"	1'07"		1'16"

the results of the effect of sodium nucleate had been previously reported,[4] these experiments were repeated for the purpose of establishing new data. Table V represents the findings of such a typical experiment. Before the experiment, all animals were tested with a histamine aerosol and were found to be reactive. Out of a group of eight passively sensitized animals receiving normal saline instead of sodium nucleate, seven developed asthma in less than two minutes and only one required as long as three minutes and thirty seconds, the mean reaction time being one minute and twenty-five seconds. On the other hand, in a group of fifteen animals receiving sodium nucleate intramuscularly, only one animal reacted in as short a time as two minutes and thirty seconds from the antigen aerosol and seven animals could stay in the chamber ten minutes or longer. Although the figure of ten minutes was the maximum used for the sake of computing the mean of seven minutes, eleven seconds, the animals that could tolerate a ten-minute exposure could stay in the aerosol practically indefinitely.

TABLE V. EFFECT OF SODIUM NUCLEATE ON ASTHMA IN GUINEA PIGS INDUCED BY AEROSOLS OF EGG ALBUMIN

	SALINE (CONTROLS)		SODIUM NUCLEATE			
Individual end points	1'15"	1'30"	10'	10'	8'30"	3'
	1'20"	3'30"	10'	2'30"	10'	5'30"
	55"	1'05"	10'	3'50"	2'40"	10'
	40"	1'05"	5'10"	6'30"	10'	
	(8 animals)			(15 animals)		
Mean	1'25"			7'11"		
	Preinjection mean histamine response: 60"			Preinjection mean histamine response: 1'04"		

In similar experiments on the effect of sodium nucleate on the histamine aerosol response, no significant influence could be noted. As will be seen from Table VI, the histamine aerosol reacting times before injection, after injection with saline, and after injection with sodium nucleate were not significantly different. In the group receiving sodium nucleate, only one animal took as long as six minutes to react.

TABLE VI. EFFECT OF SODIUM NUCLEATE ON ASTHMA IN GUINEA PIGS INDUCED BY AEROSOLS OF HISTAMINE

	SALINE (CONTROLS)		SODIUM NUCLEATE			
Individual end points	55″	1′05″	1′40″	1′25″	50″	1′45″
	40″	1′05″	1′40″	1′30″	1′30″	2′45″
	1′35″	1′45″	1′40″	6′	25″	2′05″
	1′15″	1′20″	60″	1′10″	1′05″	2′
Mean	(8 animals) 1′12″		(16 animals) 1′47″			
	Preinjection mean histamine response: 1′07″		Preinjection mean histamine response: 1′02″			

Influence of Bilateral Adrenalectomy on Sensitivity of the Guinea Pig to Antigen and Histamine Aerosols.—It is generally believed that adrenalectomized animals become much more sensitive to various stimuli, including histamine and anaphylactic challenge. This has been demonstrated quite frequently in the mouse and rat.[8] If a markedly increased sensitivity to histamine or antigen

TABLE VII. EFFECT OF BILATERAL ADRENALECTOMY ON RESPONSE TO ANTIGEN AEROSOL

	REACTION TIME IN ANIMALS RECEIVING NORMAL SALINE			REACTION TIME IN ANIMALS RECEIVING SODIUM NUCLEATE		
Individual end points	3′05″	2′	60″	4′	5′15″	7′10″
	1′05″	3′	3′30″	10′	9′	10′
	2′15″	1′45″	4′	2′30″	60″	10′
	1′30″	2′05″	2′30″	6′10″	7′15″	
	2′45″	3′30″	1′20″	1′15″	6′	
Mean	(15 animals) 2′20″			(13 animals) 6′07″		
	Presurgery mean histamine response: 1′10″			Presurgery mean histamine response: 1′45″		

prevailed in the adrenalectomized guinea pig, it would be desirable that a lesser challenge be used in order to compare it with the possible modifying effect of sodium nucleate. It was rather surprising, therefore, that we could not find an alteration of the response to antigen. Adrenalectomy had no effect on the sensitivity of guinea pigs to histamine aerosol. These findings are listed in the left-hand columns of Tables VII and VIII.

Inhibiting Effect of Sodium Nucleate on the Asthma From Antigen and Histamine Aerosols in the Adrenalectomized Guinea Pig.—The effect of pretreat-

TABLE VIII. EFFECT OF BILATERAL ADRENALECTOMY ON RESPONSE TO HISTAMINE AEROSOL

	REACTION TIME IN ANIMALS RECEIVING NORMAL SALINE			REACTION TIME IN ANIMALS RECEIVING SODIUM NUCLEATE	
Individual end points	1′20″	2′	2′	2′10″	1′10″
	1′55″	1′45″	2′40″	2′45″	2′10″
	1′15″	1′10″	50″	10′	1′45″
	1′20″	2′30″		25″	2′05″
	2′50″	35″		1′15″	
Mean	(13 animals) 1′42″			(9 animals) 2′38″	
	Presurgery mean histamine response: 1′10″			Presurgery mean histamine response: 1′09″	

ment with sodium nucleate in the adrenalectomized animals is compared also in Table VII with those receiving normal saline. Only two animals out of the thirteen treated with sodium nucleate reacted in four minutes or less, while three animals could tolerate the antigen ten minutes or longer. The results indicate that, in the absence of the adrenals, sodium nucleate still produces an inhibiting effect on the asthma induced by an antigen aerosol. Sodium nucleate had a decided effect in delaying the asthma from histamine aerosol in only one animal out of nine. These findings are illustrated in Table VIII. A summary of the results in all final experiments is listed in Table IX.

TABLE IX. SUMMARY OF RESULTS

EXPERIMENTAL GROUP	HISTAMINE AEROSOL			ANTIGEN AEROSOL		
	NUMBER OF ANIMALS	MEAN TIME	RANGE	NUMBER OF ANIMALS	MEAN TIME	RANGE
Normal controls	35	1'09"	25" to 2'10"	10	1'54"	1'05" to 3'30"
Sodium nucleate	16	1'47"	25" to 6'	15	7'11"	2'30" to 10'+
Sham surgery	16	1'01"	20" to 2'40"	12	2'14"	35" to 2'25"
Adrenalectomy	13	1'42"	35" to 2'50"	15	2'20"	1' to 4'
Adrenalectomy + Sodium nucleate	9	2'38"	25" to 10'+	13	6'07"	1' to 10'+

DISCUSSION

The experiments demonstrate that sodium nucleate injections in the guinea pig modify the asthma produced by aerosols of antigens by means other than pituitary-adrenal stimulation. This finding, if applied literally in the interpretation of all "stresses" and all animals. including man, would modify our present concept of the mechanism of "stress" effects. Whether this is true of other so-called "stresses," which we have previously shown to be inhibitors of such asthma, or whether it is true of other nonspecific procedures not yet reported, remains to be investigated. It is also important to extend investigations to other animals and possibly to man. Some of these studies are now in progress.

While the use of DOCA complicates the experiments somewhat, it should be noted that, although DOCA was administered to all the adrenalectomized animals, the inhibiting effect was evident only in those that received sodium nucleate. Unoperated and sham adrenalectomized animals also failed to be influenced by the same dose of DOCA.

The effect of sodium nucleate injection on the response to histamine aerosol remains open to some question. The results in the present series indicate that the asthma might be modified only in an occasional animal. Other experiments in the past had indicated a greater effect. At present we are planning ways and means to resolve these discrepancies. The final answer to this question is a basic one, since it can help to delineate the possible mechanisms involved in this kind of "stress." If sodium nucleate would modify the

response to both histamine and antigen aerosol, it would be inferred that the inhibiting action of sodium nucleate is on the reacting tissue. If, on the other hand, the response to the histamine aerosol were unaffected by the sodium nucleate, it would signify that the reacting tissue has not been altered. The inference would be that there has been interference with the availability of active histamine or other active substance liberated by the antigen-antibody reaction. This could be due to such factors as more rapid destruction of liberated histamine by an increase of histamine-degrading enzymes, or to other means of modifying the metabolism of histamine or other mediators producing asthma.

The present experiments indicate further that the adrenalectomized guinea pig does not become more sensitive to histamine or antigen response. Amounts of antiserum smaller than those used in nonadrenalectomized animals failed to sensitize sufficiently for a good response with the antigen. Since these results are at variance with the general concept of the effects of adrenalectomy in other species, our findings require closer scrutiny. Due to the great difficulty in obtaining a sufficient number of adrenalectomized animals for our basic experiments, we used only the dose of antigen employed in the control experiments. It is possible that a greater sensitivity in these animals might have become evident if we had been able to obtain a maximum response with smaller doses of antigen. The lower mean time after sodium nucleate injections in adrenalectomized animals as compared with the unoperated animals, might also be due to the fact that the adrenalectomized animals may be more sensitive to begin with. It is interesting to record that sodium nucleate was much more toxic to the guinea pigs after adrenalectomy.

The failure of an exploratory operation to inhibit asthma in the guinea pig differs from the effect of major surgery in man. Possibly this is an indication that the guinea pig asthma method of assay is a more severe test of inhibiting effect than that of clinical allergy in man. One might also consider the possibility that psychic factors in surgery might be a greater "stress" than the surgery itself.

SUMMARY

1. The modifying effect of sodium nucleate injections on asthma in the guinea pig produced by antigen aerosols has been confirmed.

2. A similar inhibiting effect in asthma produced by a histamine aerosol is questionable. It is possible that sodium nucleate does not alter tissue sensitivity to histamine, but perhaps interferes with the availability of the histamine or other mediator released in the antigen-antibody reaction.

3. Bilateral adrenalectomy does not appear to increase the sensitivity of the guinea pig to either an antigen or histamine aerosol.

4. The absence of adrenals in the guinea pig does not prevent the inhibiting effect from asthma produced by sodium nucleate. It is concluded that such a "stress" is not mediated by pituitary adrenocortical stimulation.

5. It is emphasized that the preceding findings apply to one "stress," sodium nucleate, and to one animal, the guinea pig. Whether similar results will be obtained with other stresses and in other species, including man, will be the subject of further investigation.

REFERENCES

1. Feinberg, S. M., Osborne, S. L., and Afremow, M. L.: Fever by Diathermy in the Treatment of Allergic Diseases, J. ALLERGY **2**: 414, 1931.
2. Malkiel, S.: The Influence of ACTH and Cortisone on Histamine and Anaphylactic Shock in the Guinea Pig, J. Immunol. **66**: 379, 1951.
3. Feinberg, S. M., and Malkiel, S.: Protective Effect of Cortisone on Induced Asthma in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **81**: 104, 1952.
4. Feinberg, S. M., Malkiel, S., and McIntire, F. C.: The Effect of Stress Factors on Asthma Induced in Guinea Pigs by Aerosolized Antigens, J. ALLERGY **24**: 302, 1953.
5. Schachter, R. J., and Bebee, M. O.: Assay of Adrenal Cortical Extract, Proc. Soc. Exper. Biol. & Med. **40**: 541, 1939.
6. Clark, W. G.: Maintenance of Adrenalectomized Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **46**: 253, 1941.
7. Freund, J., Lipton, M. M., and Thompson, G. F.: Impairment of Spermatogenesis in the Rat After Cutaneous Injection of Testicular Suspension With Complete Adjuvants, Proc. Soc. Exper. Biol. & Med. **87**: 408, 1954.
8. Dougherty, T. F., in Christman, R. C.: Pituitary Adrenal Function, Washington, 1950, American Association for the Advancement of Science, p. 79.

STUDIES IN PULMONARY VENTILATORY FUNCTION

I. Vital Capacity, First One-Second Capacity, and Forced Respiratory Curves in Patients With Asthma: Comparative Evaluation of Methods

Jean Roy, M.D.,* H. Beecher Chapin, M.D., and Jean Favre, M.D.,**
New York, N. Y.

THE vital capacity, or measurement of the total amount of air which can be exhaled after a maximum inspiration as described by Hutchinson[1] in 1846, is a simple and useful test for the rough estimation of respiratory function.[2-6] It is the purpose of this article, however, to show the greater value of dynamic tests,[7] such as the first one-second capacity and the mean rate of air flow during respiration, as indices of the efficiency of pulmonary ventilation.

The maximum breathing capacity, which has been valuable as a dynamic measure of pulmonary ventilation, is a rather cumbersome determination. Gaensler,[8] in 1951, in an attempt at simplifying the test for the clinical evaluation of pulmonary ventilation, attached a solenoid to the standard vital capacity spirometer. It was then possible to record the time-volume relationships of from one- to ten-second portions of the stroke volume measurement of the lungs. The clinical value of this test has been demonstrated repeatedly, but previous studies show that opinions in this respect differ.[9-12]

Accordingly, in this report upon normal subjects and patients with asthma, measurements of the rate of expiratory and inspiratory air flow have been evaluated.

MATERIAL

The subjects studied in this report have been placed into three general groups: the normal, the symptom-free asthmatic, and the active asthmatic, each being divided into subgroups according to sex and age (below or above 40 years).

The subjects of the normal group were volunteers from the hospital staff. The symptom-free asthmatic subjects had neither subjective complaints nor objective clinical signs at the time of the study. Some of them had been symptom-free for periods of up to five years. The duration of their disease had a range of from one to fifty years. The patients in the active asthmatic group presented mild to severe classical clinical asthmatic symptoms and signs at the time of the study. The duration of their disease had a range of

From The Institute of Allergy, The Roosevelt Hospital, New York, N. Y.
Received for publication Feb. 23, 1955.
*Present address: 5004 St. Lawrence Blvd., Montreal, Canada.
**Present address: Boismont Clinic, Vennes/Lausanne, Switzerland.

from one-tenth of one year to forty-five years. The diagnosis in all patients in the symptom-free asthmatic group and the active asthmatic group was perennial asthma, consisting of spontaneous intermittent attacks of wheezing due to intrinsic and extrinsic causes, with periods of freedom from dyspnea between the attacks. The relationship between the type of asthma and the tests discussed in this article will be presented in a subsequent article.

METHODS

By means of the Gaensler Vitalometer, vital capacity and the first one-second volume measurements were studied. The subjects, while in an upright position, were instructed to take the deepest breath possible and to exhale into the mouthpiece of the Vitalometer as rapidly and completely as possible. Three determinations were made with each subject, with a three-minute rest period between each two determinations. The determinations were obtained before and after the use of a bronchodilator agent (epinephrine, aqueous solution 1:1,000, 0.4 ml. by subcutaneous injection) upon twenty normal subjects, and before and after epinephrine upon thirty symptom-free subjects as well as twenty-nine patients with active asthma. In the normal group, the determinations after epinephrine were done upon twenty subjects only because no appreciable change was found either in the first one-second volume or in the vital capacity after the injection of epinephrine in these normal subjects. Determinations before adrenalin, however, were done upon a total of forty normal subjects. After the injection of epinephrine, the optimal time interval before repeating the determinations was found to be between fifteen and thirty minutes for the majority of cases.

TABLE I. GROUPS AND SUBGROUPS OF SUBJECTS STUDIED BY THE VITALOMETER

GROUPS	NUMBER	NUMBER OF SUBJECTS IN EACH SUBGROUP				DURATION OF DISEASE IN YEARS
		SEX		AGE IN YEARS		
		MALE	FEMALE	17 TO 39	40 TO 68	
Normal	40	20	20	20 (mean age 32)	20 (mean age 52)	
Symptom-free asthmatic	30	16	14	14 (mean age 32)	16 (mean age 58)	Range 1 to 48 (mean 11)
Active asthmatic	29	18	11	13 (mean age 31)	16 (mean age 53)	Range 1 to 45 (mean 13)

In the group with active asthma, eight patients had mild asthmatic symptoms and signs, twelve patients were moderately asthmatic, and nine were in a severe asthmatic state at the time of the study. The data concerning the groups, the number of cases in each subgroup, and the duration of the disease are given in Table I. Only the highest volume of three determinations of the first one-second volume and the vital capacity obtained by forced maximal expiration were recorded for each subject, correction having been made for body temperature, water vapor saturation, and ambient pressure. The predicted vital capacity was found for each subject according to the formulas of Baldwin, Cournand, and Richards.[13] No correction was made for the upright

TABLE II. PREDICTED VITAL CAPACITY, DETERMINED FIRST ONE-SECOND VOLUME, AND VITAL CAPACITY. MAXIMAL FORCED EXPIRATION. RESULTS IN EACH SUBGROUP IN MILLILITERS (37° C. SAT.).

SUBJECTS				PREDICTED VITAL CAPACITY*			DETERMINED											
							FIRST ONE-SECOND VOLUME						TOTAL VOLUME					
							BEFORE EPINEPHRINE			AFTER EPINEPHRINE†			BEFORE EPINEPHRINE			AFTER EPINEPHRINE†		
GROUPS	SEX	AGE (YEARS)	NO.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.
Normal	M	50 to 39	10	4,182	±238	± 79	3,850	±603	±201		‡		4,481	± 618	±206		‡	
	M	40 to 63	10	3,672	±159	± 53	3,073	±653	±218				3,566	± 582	±194			
	F	17 to 39	10	2,871	±212	± 71	2,787	±277	± 92				3,105	± 301	±100			
	F	40 to 67	10	2,552	±167	± 56	2,192	±374	±125				2,668	± 309	±103			
Symptom-free asthmatic	M	20 to 39	8	4,291	±577	±217	3,469	±784	±294	3,936	± 702	±264	4,396	± 486	±183	4,484	± 541	±206
	M	40 to 67	8	3,523	±237	± 89	2,257	±807	±303	2,417	± 916	±344	3,310	± 766	±288	3,509	± 491	±185
	F	20 to 39	6	2,763	±124	± 55	2,281	±301	±134	2,612	± 268	±119	2,783	± 440	±196	2,998	± 278	±124
	F	40 to 68	8	2,554	±151	± 57	1,357	±611	±230	1,683	± 469	±178	1,784	± 734	±276	2,182	± 613	±230
Active asthmatic	M	18 to 39	9	4,200	±484	±171	1,636	±784	±273	2,302	±1008	±356	2,740	±1012	±358	3,550	±1115	±394
	M	40 to 60	9	3,705	±148	± 52	1,501	±519	±183	2,086	± 841	±297	2,753	± 795	±281	3,397	± 893	±316
	F	20 to 39	4	3,032	§		1,164			1,378			1,986			2,187		
	F	40 to 61	7	2,612	±170	± 69	1,479	±414	±169	1,903	± 462	±189	2,211	± 654	±267	2,555	± 568	±232

M.V., Mean volume; S.D., standard deviation; S.E., standard error of the mean.

*Predicted vital capacity calculated according to Baldwin, Cournand, and Richards[13] formula.

†Determinations done twenty minutes after subcutaneous injection of 0.4 ml. of epinephrine 1:1,000.

‡No appreciable change was found in determined capacities upon twenty normal subjects after the injection of 0.4 ml. of epinephrine 1:1,000.

§No statistical measurement was done for this small subgroup.

TABLE III. PREDICTED VITAL CAPACITY, DETERMINED FIRST ONE-SECOND VOLUME, AND VITAL CAPACITY. MAXIMAL FORCED EXPIRATION. RESULTS IN EACH GROUP IN MILLILITERS (37° C. SAT.)

SUBJECTS		PREDICTED VITAL CAPACITY*			DETERMINED											
					FIRST ONE-SECOND VOLUME						TOTAL VOLUME					
					BEFORE EPINEPHRINE			AFTER EPINEPHRINE†			BEFORE EPINEPHRINE			AFTER EPINEPHRINE†		
GROUPS	NUMBER	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.
Normal	40	3,319	±672	±108	2,976	± 781	±125		‡		3,445	± 824	±132		‡	
Symptom-free asthmatic	30	3,317	±774	±142	2,345	±1027	±191	2,665	±1065	±198	3,087	±1160	±215	3,313	±998	±185
Active asthmatic	29	3,502	±689	±130	1,491	± 643	±121	2,011	± 875	±165	2,512	± 927	±175	3,074	±488	± 92

M.V., Mean volume; S.D., standard deviation; S.E., standard error of the mean.

*Predicted vital capacity calculated according to Baldwin, Cournand, and Richards[13] formula.

†Determinations done twenty minutes after subcutaneous injections of 0.4 ml. of epinephrine 1:1,000.

‡No appreciable change was found in determined capacities upon twenty normal subjects after the injection of 0.4 ml. of epinephrine 1:1,000.

position of the subject during the test. Mean volumes were calculated for each group of subjects from the data representing the predicted individual vital capacities and the determined first one-second and determined vital capacities. These mean volumes, expressed in milliliters, are recorded with their standard deviations and their standard errors. No statistical measurement was feasible for the small group of four women between the ages of 20 and 39 years with active asthma (Tables II and III). The mean volumes of the determined first one-second capacities and the vital capacities were converted to percentages of the mean predicted vital capacities (Table IV).

TABLE IV. EVALUATION OF FIRST ONE-SECOND VOLUME AND VITAL CAPACITY (RESULTS EXPRESSED AS PERCENTAGE OF PREDICTED VITAL CAPACITY)

SUBJECTS		FIRST ONE-SECOND CAPACITY		DETERMINED VITAL CAPACITY	
GROUPS	NUMBER	BEFORE EPINEPHRINE (PER CENT)	AFTER EPINEPHRINE (PER CENT)	BEFORE EPINEPHRINE (PER CENT)	AFTER EPINEPHRINE (PER CENT)
Normal	40	89.6		102.9	
Symptom-free asthmatic	30	69.6	80.2	91.2	98.3
Active asthmatic	29	43.6	57.4	72.4	86.5

Graphic tracings of maximal forced expiration and inspiration were obtained with a Benedict-Roth spirometer whose excursions were recorded by means of a kymograph whose speed could be regulated at rates of from 20 to 150 mm. per second. Time was recorded upon the rapidly moving kymograph paper beneath the tracing by means of a Franz Kymoelectric timer. With this apparatus, two expiratory and inspiratory tracings of maximal forced expiration and inspiration were obtained, before and after the injection of epinephrine, upon each subject except upon the normal subjects, on whom the determinations were done only before epinephrine for the reasons stated previously. The subjects were in an upright position, with nose clips applied. A standard rubber mouthpiece, with tube diameter of 0.5 inch, was placed between their lips and teeth. The subjects were allowed to breathe room air to permit them to become accustomed to the mouthpiece while instructions were given in the procedure of the test. Uncooperative subjects were excluded from the study. The valve of the spirometer was opened immediately preceding the start of the inspiratory or expiratory phase.

The graphic tracings of forced maximal expiration and inspiration to obtain measurements of the total time and total volume of these phases of the ventilatory cycle were taken from a total of 112 subjects: forty normal, thirty-seven symptom-free asthmatic, and thirty-five active asthmatic subjects. In the active asthmatic group, fourteen patients had mild symptoms, fourteen had moderate symptoms and seven had severe symptoms. The data concerning the groups, the number of subjects in each subgroup, and the duration of their disease are shown in Table V. The total volume of air expired and inspired and the total time of each respiratory phase were measured on graph paper.

The mean rate of flow of expiration and inspiration then was found by dividing the total volume by total time. Mean total volumes, mean total times, and mean volumes per unit of time were obtained for each subgroup of subjects. These mean values, expressed as milliliters and seconds, are shown with their standard deviations and their standard errors in Table VI.

TABLE V. GROUPS AND SUBGROUPS OF SUBJECTS. STUDY OF GRAPHIC TRACINGS OF FORCED RESPIRATION BY MEANS OF BENEDICT-ROTH SPIROMETER

SUBJECTS		NUMBER OF SUBJECTS IN EACH SUBGROUP				DURATION OF DISEASE IN YEARS
		SEX		AGE IN YEARS		
GROUPS	NUMBER	MALE	FEMALE	18 TO 39	40 TO 67	
Normal	40	20	20	20 (mean age 29)	20 (mean age 49)	
Symptom-free asthmatic	37	18	19	19 (mean age 28)	18 (mean age 51)	Range 1 to 50 (mean 17)
Active asthmatic	35	17	18	16 (mean age 31)	19 (mean age 53)	Range 0.1 to 35 (mean 11)

RESULTS

The mean first one-second volume and the determined mean vital capacity, as calculated from the measurements obtained by means of the Vitalometer, expressed as percentage of predicted vital capacity of forty normal subjects, gave respective mean values of 89.6 per cent and 102.9 per cent. This is to be compared to 69.6 per cent and 91.2 per cent of thirty symptom-free asthmatic patients and to 43.6 per cent and 72.4 per cent of twenty-nine active asthmatic patients before epinephrine. After epinephrine, no appreciable change was found in twenty normal subjects. In the symptom-free asthmatic group, after epinephrine, there was an increase of 10.6 per cent for the mean first one-second volume and an increase of 7.1 per cent for the mean vital capacity. After epinephrine, in the group with active asthma, there was an increase of 13.8 per cent for the mean first one-second capacity and of 14.1 per cent for the mean vital capacity (Table IV).

From these data, it is seen that the first one-second volume is impaired to a greater extent than the vital capacity in these groups of subjects with asthmatic disease. Moreover, an examination of individual results of the fifty-nine asthmatic patients shows a decrease from the predicted normal value of the first one-second volume in fifty-five cases, compared to a decrease from the predicted normal value of the vital capacity in forty-eight cases. After epinephrine, the total vital capacity was decreased in only thirty-two cases, while forty-seven cases still showed impairment of the first one-second volume.

For the purpose of evaluating the relationships of time and volume determined by graphic tracing with the Benedict-Roth apparatus and rapidly moving kymograph, assuming that the vital capacity of each subject was 100 per cent, mean curves were plotted, the points in time being placed along the abscissa, while points representing 25 per cent, 50 per cent, 75 per cent, 90 per cent, and 100 per cent of the vital capacity were placed on the ordinate (Figs. 1, 2, 3, and 4). Fig. 5 shows the relationship of these time-volume

TABLE VI. VOLUME, TIME, MEAN RATE OF FLOW DETERMINED BEFORE

SUBJECTS				PREDICTED VITAL CAPACITY	DETERMINED					
					BEFORE EPINEPHRINE			AFTER EPINEPHRINE		
GROUP	SEX	AGE (YEARS)	NO.		M.V.	S.D.	S.E.	M.V.	S.D.	S.E.
										Maximal
Normal	M	20 to 39	10	4,309	4,179	± 776	±259		†	
	M	40 to 67	10	3,738	3,754	± 814	±271			
	F	19 to 39	10	3,073	2,891	± 402	±134			
	F	40 to 56	10	2,635	2,369	± 410	±137			
Symptom-free asthmatic	M	18 to 39	10	4,284	4,524	± 888	±296	4,683	± 825	±275
	M	40 to 64	8	3,758	3,465	±1323	±500	3,556	±1246	±471
	F	18 to 39	9	2,960	2,859	± 337	±119	2,960	± 998	±353
	F	40 to 57	10	2,649	2,291	± 384	±128	2,463	± 204	± 68
Active asthmatic	M	20 to 39	7	4,219	3,256	±1068	±436	3,801	± 808	±330
	M	40 to 65	10	3,607	2,322	± 710	±237	2,889	± 706	±252
	F	20 to 39	9	2,967	2,135	± 464	±164	2,989	± 612	±216
	F	40 to 59	9	2,655	2,037	± 713	±252	2,277	± 701	±248
										Maximal
Normal	M	20 to 39	10	4,309	4,304	± 832	±277		†	
	M	40 to 67	10	3,738	3,851	± 918	±306			
	F	19 to 39	10	3,073	3,037	± 450	±151			
	F	40 to 56	10	2,635	2,489	± 319	±106			
Symptom-free asthmatic	M	18 to 39	10	4,284	4,579	± 891	±297	4,710	± 810	±270
	M	40 to 64	8	3,758	3,385	±1135	±429	3,721	±1124	±425
	F	18 to 39	9	2,960	2,813	± 320	±113	2,953	± 356	±126
	F	40 to 57	10	2,649	2,425	± 348	±116	2,554	± 234	± 78
Active asthmatic	M	20 to 39	7	4,219	3,598	± 748	±305	4,167	± 534	±218
	M	40 to 65	10	3,607	2,569	± 840	±280	2,970	± 859	±286
	F	20 to 39	9	2,967	2,667	± 517	±183	3,012	± 594	±210
	F	40 to 59	9	2,655	2,151	± 734	±259	2,326	± 790	±279

factors between forced maximal inspiration and expiration on normal subjects and between inspiration on the group of subjects who were symptom-free and the group with active asthma before epinephrine. The Benedict-Roth apparatus with the kymograph offered more resistance to the respiratory effort of the subjects in all groups than did the Vitalometer, as is shown, for instance, by the results obtained for the group of normal subjects, whose determined mean vital capacity was 95.9 per cent of their mean predicted vital capacity, compared to 102.9 per cent. This was so, even though the accessory mechanism of the Benedict-Roth spirometer to record the expiratory volume was removed to diminish the resistance of this apparatus during the test. For the symptom-free asthmatic group and the active asthmatic group, the respective determined mean vital capacities were found to be equivalent to 96.2 per cent and 76.2 per cent of their respective mean predicted vital capacities. After epinephrine, the improvement in the mean vital capacity in these two groups was, respectively, 3.8 per cent and 12.2 per cent, thus giving the symptom-free asthmatic group a mean vital capacity of 100 per cent and the active asthmatic group a mean vital capacity of 88.4 per cent. The mean total time of expiration for the normal subjects was 2.58 seconds, compared to 5.17 seconds for the symptom-free asthmatic group and 7.08

AND AFTER THE USE OF EPINEPHRINE* (RESULTS UPON 112 SUBJECTS)

MEAN TIME IN SECONDS						MEAN VOLUME IN MILLILITERS PER 0.1 SECOND					
BEFORE EPINEPHRINE			AFTER EPINEPHRINE			BEFORE EPINEPHRINE			AFTER EPINEPHRINE		
SECONDS	S.D.	S.E.	SECONDS	S.D.	S.E.	M.V.	S.D.	S.E.	M.V.	S.D.	S.E.
Forced Expiration											
2.18	±0.63	±0.21		†		208	±71	±24		†	
2.86	±0.90	±0.30				143	±46	±15			
2.42	±0.72	±0.24				127	±31	±10			
2.88	±0.69	±0.23				89	±32	±11			
5.78	±3.58	±1.19	4.34	±2.28	±0.76	116	±69	±23	134	±57	±19
6.95	±1.4	±0.53	5.50	±1.29	±0.64	50	±19	± 7	72	±37	±14
3.98	±2.23	±0.79	3.09	±1.67	±0.59	94	±42	±15	121	±48	±17
3.98	±1.65	±0.55	4.24	±2.10	±0.70	76	±51	±17	75	±42	±14
6.91	±3.1	±1.26	5.74	±2.58	±1.05	52	±17	± 7	85	±51	±21
9.40	±3.5	±1.16	10.30	±3.22	±1.07	30	±21	± 7	35	±25	± 8
5.93	±3.1	±1.09	3.77	±1.88	±0.66	56	±25	± 9	94	±35	±13
6.06	±1.26	±0.45	6.00	±2.15	±0.76	34	±14	± 5	46	±28	±10
Forced Inspiration											
1.60	±0.44	±0.15		†		275	±61	±20		†	
1.50	±0.27	±0.09				259	±50	±17			
1.50	±0.27	±0.09				208	±39	±13			
1.62	±0.50	±0.17				174	±46	±15			
1.72	±0.39	±0.13	1.56	±0.30	±0.10	284	±93	±31	307	±60	±20
1.52	±0.32	±0.12	1.50	±0.21	±0.08	229	±79	±30	250	±77	±29
1.56	±0.37	±0.13	1.24	±0.11	±0.04	189	±40	±14	240	±37	±13
1.42	±0.27	±0.09	1.40	±0.42	±0.14	177	±45	±15	194	±48	±16
1.74	±0.33	±0.14	1.63	±0.33	±0.14	210	±50	±20	263	±45	±18
1.62	±0.29	±0.10	1.70	±0.35	±0.12	164	±68	±23	182	±64	±21
1.62	±0.51	±0.18	1.56	±0.54	±0.19	179	±53	±19	212	±70	±24
1.62	±0.46	±0.16	1.47	±0.38	±0.13	141	±55	±19	162	±53	±19

M.V., Mean volume; S.D., standard deviation; S.E., standard error of the mean.
*Determinations done twenty minutes after subcutaneous injection of 0.4 ml. of epinephrine 1 :1,000.
†Experiment not done on normal subjects after the use of epinephrine.

seconds for the active asthmatic group. After epinephrine, in both asthmatic groups, the mean total time decreased to 4.29 seconds for the symptom-free asthmatic group and to 6.45 seconds for the active asthmatic group.

A comparison of results in these three groups of subjects emphasized the equal importance of both volume and time of expiration in the evaluation of respiratory efficiency of the asthmatic subjects. That one or both of these factors might be impaired led to the conclusion that the expression of the mean rate of flow would be more representative of the ventilatory efficiency. The mean volume per 0.1 second was calculated for each group of subjects and expressed as per cent of the mean predicted vital capacity. In the group of normal subjects, this index was found to be 4.12 per cent, compared to 2.46 per cent for the symptom-free asthmatic group and 1.27 per cent for the active asthmatic group. After epinephrine, the mean rate of flow increased in both asthmatic groups (Table VII).

In inspiration, it has long been recognized that in normal subjects the volume of air inspired equaled fairly closely the volume of air expired and that the time ratio between expiration and inspiration was represented by a

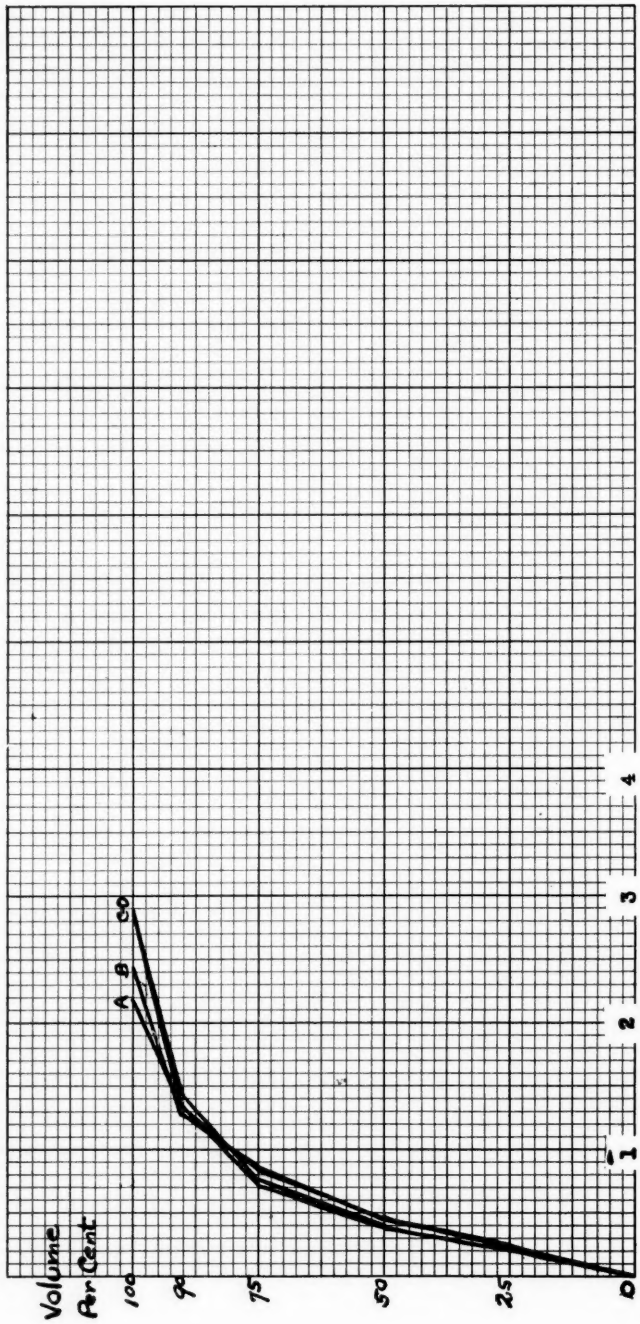


Fig. 1.—Mean curves of forced maximal expiration upon normal subjects. *A*, Men, aged 20 to 39 years; *B*, women, aged 20 to 39 years; *C*, men, aged 40 to 67 years; *D*, women, aged 40 to 56 years.

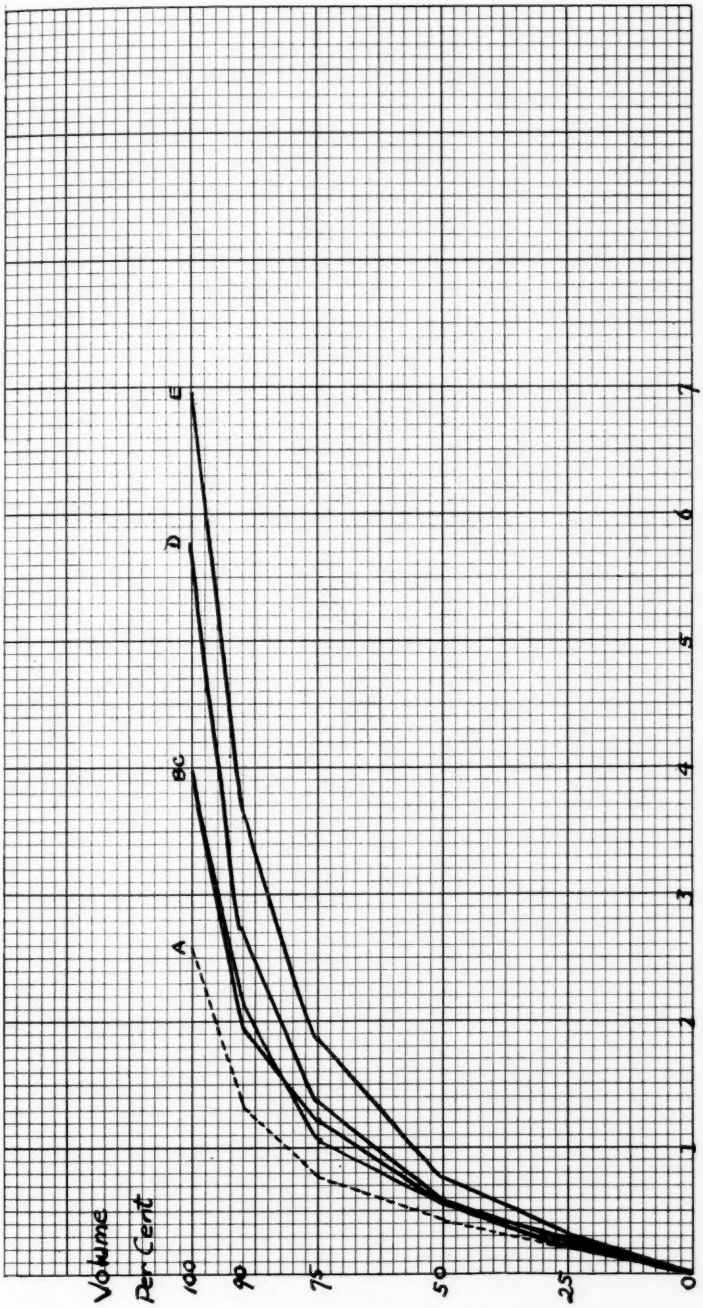


Fig. 2.—Mean curves of forced maximal expiration upon symptom-free asthmatic subjects before epinephrine. *A*, Normal group; *B*, women, aged 18 to 39 years (symptom-free group); *C*, women, aged 40 to 59 years (symptom-free group); *D*, men, aged 20 to 39 years (symptom-free group); *E*, men, aged 40 to 64 years (symptom-free group).

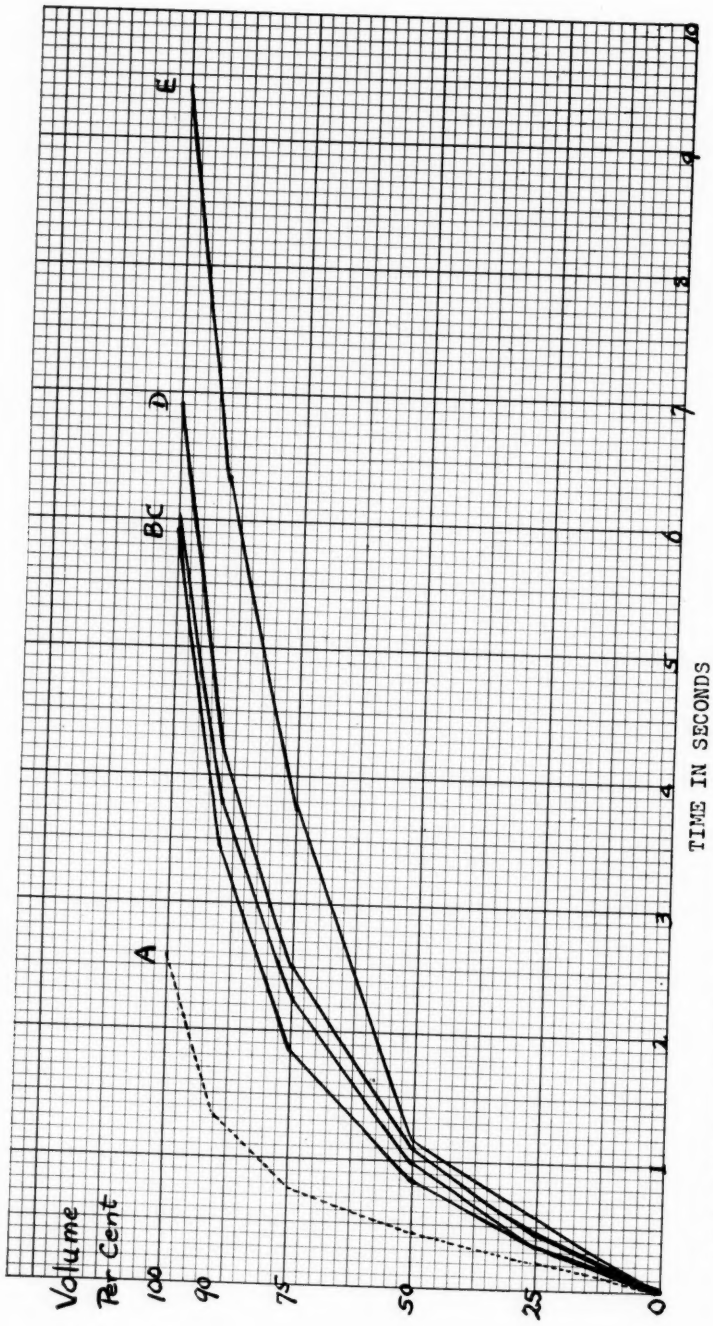


Fig. 3.—Mean curves of forced maximal expiration upon active asthmatic subjects before epinephrine. *A*, Normal group; *B*, women, aged 20 to 39 years (active asthmatic group); *C*, women, aged 40 to 59 years (active asthmatic group); *D*, men, aged 20 to 39 years (active asthmatic group); *E*, men, aged 40 to 65 years (active asthmatic group).

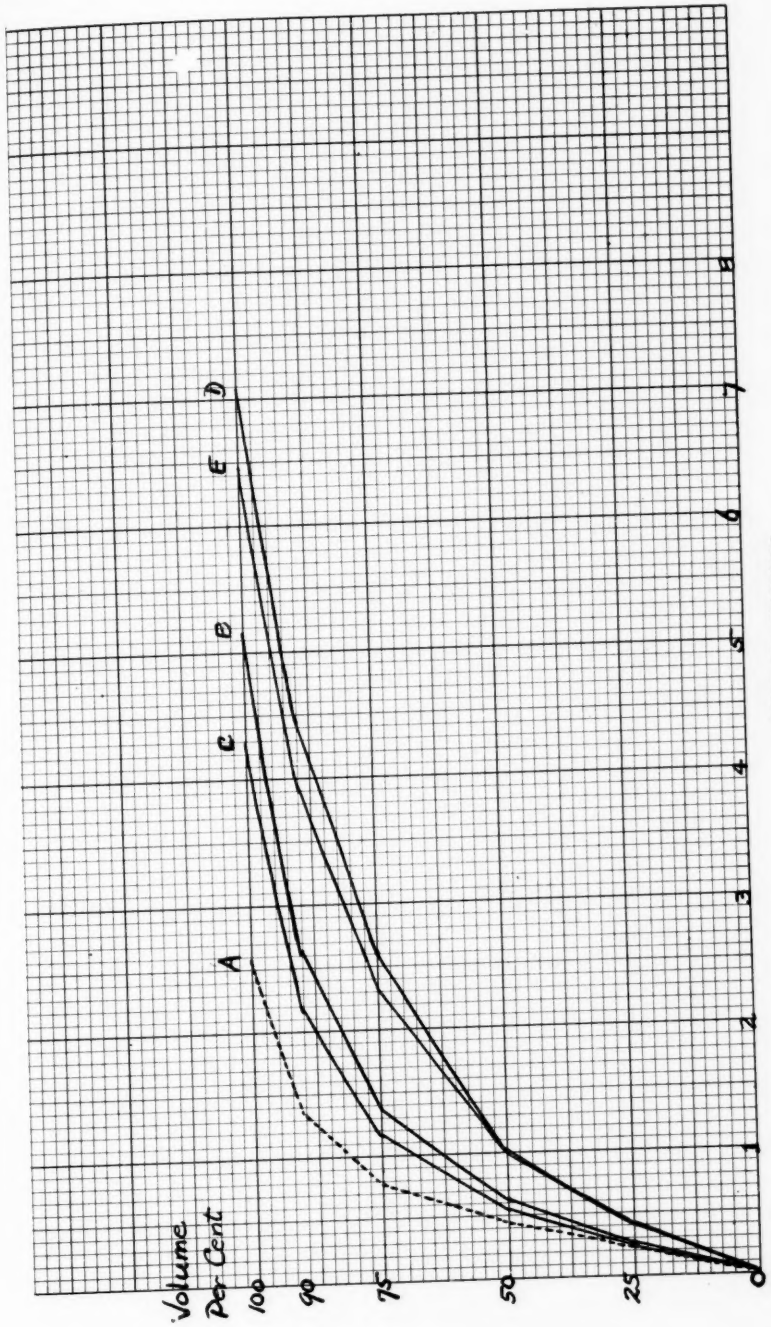


Fig. 4.—Mean curves of forced maximal expiration upon normal symptom-free asthmatic and active asthmatic subjects and after epinephrine. *A*, Normal group; *B*, symptom-free asthmatic, before epinephrine, male and female; *C*, symptom-free asthmatic, after epinephrine, male and female; *D*, active asthmatic, before epinephrine, male and female; *E*, active asthmatic, after epinephrine, male and female.

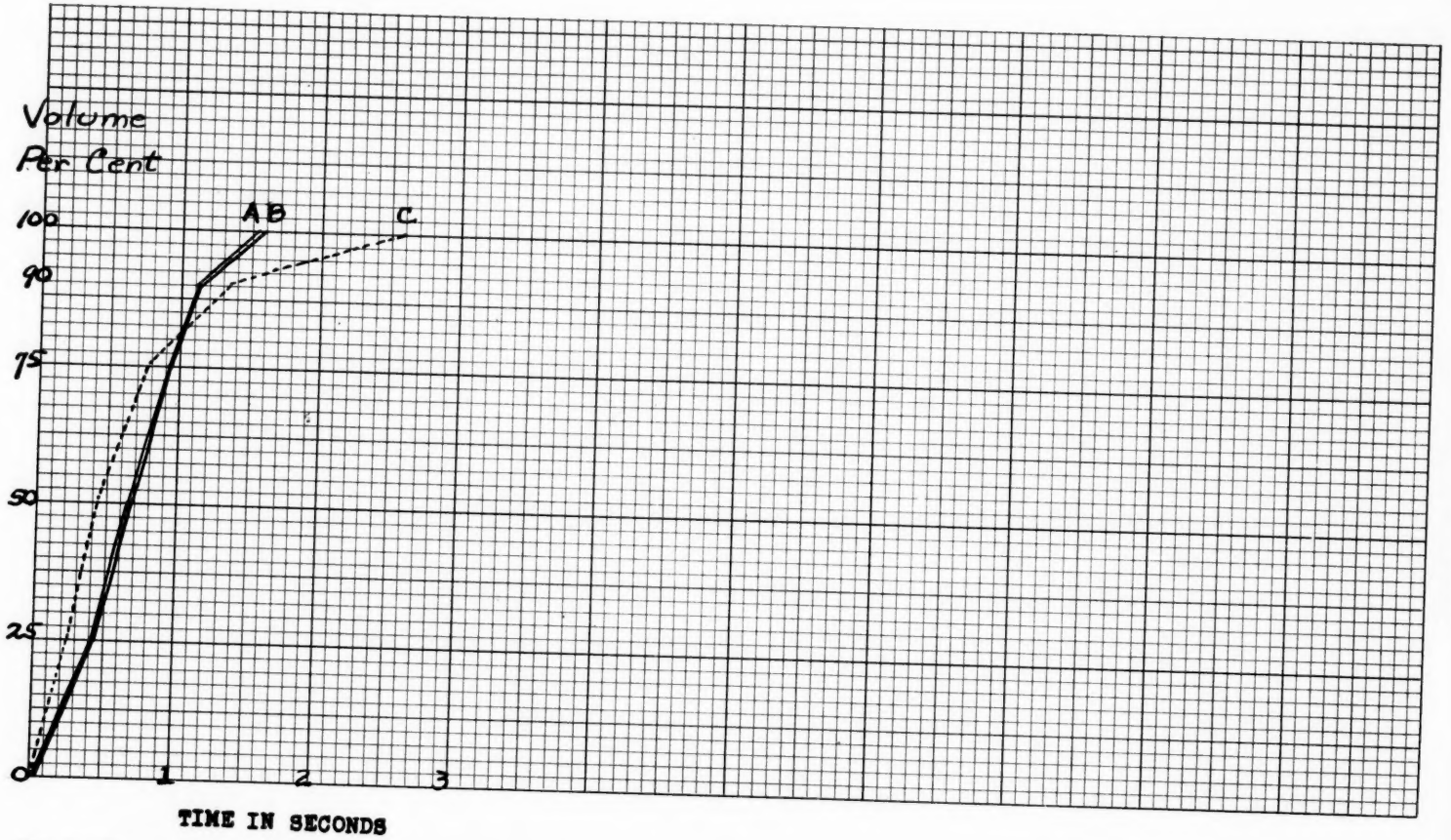


Fig. 5.—Mean curves of forced maximal inspiration upon normal, symptom-free, and active asthmatic subjects before epinephrine. *A*, Inspiration, normal group; *B*, inspiration, symptom-free asthmatic and active asthmatic groups; *C*, expiration, normal group.

TABLE VII. EVALUATION OF VITAL CAPACITY, TOTAL TIME, AND MEAN RATE OF FLOW IN TIMED MEASUREMENTS OF VITAL CAPACITY

SUBJECTS		BEFORE EPINEPHRINE			AFTER EPINEPHRINE		
GROUPS	NUMBER	MEAN DETERMINED VITAL CAPACITY (PER CENT)*	MEAN TOTAL TIME (SECONDS)	MEAN DETERMINED VOLUME PER 0.1 SECOND (PER CENT)†	MEAN DETERMINED VITAL CAPACITY (PER CENT)*	MEAN TOTAL TIME (SECONDS)	MEAN DETERMINED VOLUME PER 0.1 SECOND (PER CENT)†
		Forced Maximal Expiration					
Normal	40	95.9	2.58	4.12			
Symptom-free asthmatic	37	96.2	5.17	2.46	100	4.29	2.93
Active asthmatic	35	76.2	7.08	1.27	88.4	6.45	1.92
		Forced Maximal Inspiration					
Normal	40	99.4	1.56	5.9			
Symptom-free asthmatic	37	96.7	1.56	6.4	100.4	1.44	7.2
Active asthmatic	35	81.2	1.65	5.1	92.2	1.59	5.9

*Mean determined vital capacity expressed as percentage of mean predicted vital capacity.
†Mean determined volume per 0.1 second expressed as percentage of the mean predicted vital capacity.

constant value equivalent to 1.2.[14] The results obtained by graphic tracings of forced maximal inspiration were studied in each group and subgroup of subjects. Comparison of these results was made with those given by the forced maximal expiratory vital capacity, the total time taken for the expiratory phase, and the mean rate of flow during the expiratory effort. The mean volume of air inspired by forced maximal inspiration was expressed in the percentages of the mean predicted vital capacity for each group of subjects. A respective value of 99.4 per cent was found for the normal group, 96.7 per cent for the symptom-free asthmatic group, and 81.2 per cent for the active asthmatic group of subjects, compared to 95.9 per cent, 96.2 per cent, and 76.2 per cent, respectively, for expiration. The increase in volume of inspiration after the use of epinephrine was similar to that observed for forced maximal expiration. The mean total time for forced maximal inspiration varied from 1.56 to 1.65 seconds for the three groups of subjects and showed no significant difference between the normal and asthmatic groups. The mean rate of flow was decreased slightly for the active asthmatic group as compared to the normal group of subjects, because of the smaller stroke volume of the inspiratory effort. Expressed as a ratio of the respective mean predicted vital capacity, the value was 5.9 per cent for the normal group, 6.4 per cent for the symptom-free asthmatic group, and 5.1 per cent for the active asthmatic group of subjects. Compared to the indices for the mean expiratory rate of flow, these values are increased in both asthmatic groups.

DISCUSSION

In this study of ventilatory function, the volume and the time relationships were observed during the performance of an inspiratory or expiratory

maximal effort. Three sets of values were obtained for purposes of comparison—the first one-second volume, the mean rate of flow, and the vital capacity. Thus, a means of studying the relative efficiency of the tests as a measure of pulmonary ventilatory function was possible. The predicted vital capacity served as a fixed standard value to which the observations could be related. Thus, by relating the mean values to the constant standard values, the measurements from the various groups of subjects could be related to each other by noting the variation of the mean values of the asthmatic subjects from those of the normal group of subjects. The relationships for expiratory values are shown in Table VIII. There was too slight a variation in the inspiratory values to justify their inclusion in this table. In the symptom-free group, the mean rate of flow before and after epinephrine was 59.8 per cent and 71.1 per cent, respectively, of the mean rate of flow value found in normal subjects. In the active asthmatic group, it was 30.8 per cent before epinephrine and 46.6 per cent after epinephrine. The degree of improvement in ventilation after epinephrine is greatest in the active asthmatic subjects, averaging 14.9 per cent improvement for the three tests. The improvement in the symptom-free asthmatic group after epinephrine is 10.0 per cent.

The value representing vital capacity measurements shows the least impairment of function, even in the active asthmatic group—70.4 per cent of normal before epinephrine and 84.1 per cent after epinephrine—thus leading to the conclusion that, of the three tests, the vital capacity measurement is the least sensitive measurement of impairment of ventilatory function. The value representing the first one-second volume stands between those of the two other tests, suggesting that it is a more sensitive test than the vital capacity but a less sensitive test than the mean rate of flow. The mean rate

TABLE VIII. IMPAIRMENT OF VENTILATORY FUNCTION OF SYMPTOM-FREE ASTHMATIC AND ACTIVE ASTHMATIC SUBJECTS EXPRESSED AS PERCENTAGE OF VITAL CAPACITY-TIME VALUES FOR NORMAL SUBJECTS

	SYMPTOM-FREE ASTHMATIC SUBJECTS		ACTIVE ASTHMATIC SUBJECTS	
	BEFORE EPINEPHRINE (PER CENT)	AFTER EPINEPHRINE (PER CENT)	BEFORE EPINEPHRINE (PER CENT)	AFTER EPINEPHRINE (PER CENT)
Vital capacity	88.6	95.5	70.4	84.1
First one-second capacity	77.7	89.5	48.7	64.1
Mean rate of flow	59.8	71.1	30.8	46.6

of flow, demonstrating the greatest impairment of function and capable of demonstrating as a test a wider range of defect of ventilatory function, appears to be the most sensitive of the three tests studied for ventilatory function. It is suggested, by a statistical study of the group segregation, that the mean rate of flow may be of greater significance as a test of ventilatory function in age groups of men and women over 40 years than in those age groups of men and women under 40 years of age.

SUMMARY

1. Time and volume measurements of ventilatory function have been obtained on 211 subjects, utilizing Gaensler's apparatus and graphic tracings of forced maximal expiration and inspiration by means of a Benedict-Roth spirometer and rapidly moving kymograph with timer. These determinations were obtained before and twenty minutes after the subcutaneous injection of epinephrine.

2. A comparison of the ventilatory function of normal, symptom-free asthmatic, and active asthmatic subjects is given by relating the values for the mean determined vital capacity, the mean first one-second volume, and the mean rate of flow to the mean predicted vital capacity of each group, and by relating these expressions of the predicted vital capacity of the symptom-free group and active asthma group to that of the normal group. The results of these comparisons suggest that the relationship of the forced maximal vital capacity and time of performance of the expiratory ventilatory effort, as expressed by the mean rate of flow, is a more complete reflection of the ventilatory state than either vital capacity or the first one-second volume measurement, especially in the group of men and women over 40 years of age. The mean rate of flow, expressed as per cent of mean predicted vital capacity, was 5.9 per cent for forced inspiration and 4.12 per cent for forced expiration in the group of normal subjects. In the symptom-free asthmatic group, it was 6.4 per cent for forced inspiration and 2.46 per cent for forced expiration. In the active asthmatic group, it was 5.1 per cent for forced inspiration and 1.27 per cent for forced expiration.

A comparison of similar studies of the inspiratory phase of forced respiration, utilizing volume, total time, and mean rate of flow measurements, reveals too little variation in observations between groups for statistical significance.

The authors wish to express gratitude to Dr. Daniel Horn, the American Cancer Society, and to Rolland Lamothe, M.A., statistician at the National Industrial Conference Board, New York, for their interest and assistance.

REFERENCES

1. Hutchinson, J.: On the Capacity of the Lungs and on the Respiratory Functions, With a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Tr. Med.-Chir. Soc. London **56**: 676, 1846.
2. Cournand, A., Richards, D. W., Jr., and Darling, R. G.: Graphic Tracings of Respiration in Study of Pulmonary Disease, Am. Rev. Tuberc. **40**: 487, 1939.
3. Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency. II. The Effects of Various Types of Collapse Therapy Upon Cardio-Pulmonary Function, Am. Rev. Tuberc. **44**: 123, 1941.
4. Gross, D.: Investigations Concerning Vital Capacity, Am. Heart J. **25**: 335, 1943.
5. Gaensler, E. A.: Air Velocity Index: A Numerical Expression of the Functionally Effective Portion of Ventilation, Am. Rev. Tuberc. **62**: 17, 1950.
6. Herschfus, J. A., Bresnick, E., and Segal, M. S.: Pulmonary Function Studies in Bronchial Asthma. I. In the Control State; II. After Treatment, Am. J. Med. **14**: 23, 1953.
7. Comroe, J. H., Jr.: Specific Tests of Pulmonary Function, Methods in Medical Research, vol. 2, Chicago, 1950, The Year Book Publishers, Inc., p. 181.
8. Gaensler, E. A.: An Instrument for Dynamic Vital Capacity Measurements, Science **114**: 444, 1951.
9. Gaensler, E. A.: Analysis of the Ventilatory Defect by Timed Capacity Measurements, Am. Rev. Tuberc. **64**: 256, 1951.

10. Lowell, F. C., Schiller, I. W., Leard, S. E., and Franklin, W.: Prolonged Treatment of Bronchial Asthma With Cortisone, J. ALLERGY **24**: 112, 1953.
11. Dulfano, M. J., Herschfus, J. A., and Segal, M. S.: Timed Vital Capacity in Bronchial Asthma, J. ALLERGY **24**: 309, 1953.
12. Lowell, F. C., and Schiller, I. W.: Significance of Changes in the Expiratory Rate Observed During Measurement of the Vital Capacity in Asthma, J. ALLERGY **24**: 492, 1953.
13. Baldwin, E. D., Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency. I. Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects, Medicine **27**: 243, 1948.
14. Comroe, J. H., Jr.: Interpretation of Commonly Used Pulmonary Function Tests, Am. J. Med. **10**: 356, 1951.

EFFECT OF THE HISTAMINE LIBERATOR 48/80 IN HISTAMINE-SENSITIVE MICE

L. S. KIND, PH.D., CHARLESTON, S. C.

INVESTIGATION of the actions of histamine liberators may be of value in explaining mechanisms operative in allergic responses. Compound 48/80, a condensation product of p-methoxyphenylethyl methylamine and formaldehyde, is a particularly potent histamine liberator.[1-4] However, all of the actions of 48/80 cannot be accounted for on the basis of its ability to release histamine from tissues. The injection or inhalation of this compound fails to produce asthma or emphysema as is commonly seen in anaphylactic or histamine intoxication of guinea pigs.[5] Neoantergan does not prevent the increase in capillary permeability which follows the intradermal injection of 48/80 into guinea pigs.[6] Rats exhibit an edema syndrome from injections of 48/80, but not from injections of histamine.[7] The results reported in this article suggest that an additional property of 48/80, namely, its toxicity in mice, is also not due to the release of histamine. Mice were employed in our experiments, as certain strains of these animals become very sensitive to histamine after previous inoculation with *Hemophilus pertussis* vaccine.[8] We thus were able to compare the lethal effect of 48/80 in pertussis-inoculated, histamine-sensitive mice with the lethal effect of this compound in uninoculated, histamine-resistant mice.

MATERIALS AND METHODS

Female 20- to 30-gram white mice purchased from Tumblebrook Farms were employed. Thirty-six mice were injected intraperitoneally with 0.1 ml. of *H. pertussis* vaccine* containing 48.8 billion organisms per milliliter. Five days later the animals were divided into groups of six and each group was challenged intraperitoneally with either a dose of histamine or a dose of 48/80. Deaths were recorded over a twenty-four-hour period. The LD50 doses of histamine and of 48/80 and their confidence limits were calculated by the method of Litchfield and Wilcoxon.[9]

RESULTS AND DISCUSSION

The data in Table I indicate that the LD50 of 48/80 was 6.5 mg. per kilogram in uninoculated mice and 4.8 mg. per kilogram in pertussis-inoculated mice. Since the confidence limits of these values do not overlap, they are significantly different ($p = .05$). The LD50 of histamine in uninoculated mice was 1,100 mg. per kilogram, as compared with only 4.1 mg. per kilogram in pertussis-injected animals.

From the Department of Bacteriology, Medical College of South Carolina, Charleston, South Carolina.

This investigation was supported by Research Grant E 372 (C2) from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

Received for publication May 9, 1955.

*Obtained through the courtesy of J. Munoz, Sharp & Dohme.

Pertussis-injected mice were thus 268 times more sensitive to the lethal effects of histamine than were the uninoculated control animals; however, the pertussis-inoculated mice were only 1.3 times more sensitive to the fatal effect of

TABLE I. MEDIAN LETHAL DOSES OF 48/80 IN HISTAMINE-SENSITIVE AND HISTAMINE-RESISTANT MICE

	HISTAMINE HYDROCHLORIDE (MG./KG.)	SURVIVORS PER TOTAL INJECTED	LD50 AND 19/20 CONFIDENCE LIMITS (MG./KG.)	48/80 (MG./KG.)	SURVIVORS PER TOTAL INJECTED	LD50 AND 19/20 CONFIDENCE LIMITS (MG./KG.)
Pertussis-inoculated mice	2.5	5/6		3.75	6/6	
	5	3/6	4.1 (2.7-6.2)	4.5	5/6	4.8 (4.4-5.2)
	8	0/6		5	1/6	
Uninoculated mice	875	5/6		5	6/6	
	1250	1/6	1100 (916-1320)	6	4/6	6.5 (5.9-7.2)
	1500	1/6		7.5	1/6	

48/80. Thus, it seems likely that the lethal effects of 48/80 in mice are not due, to any great extent, to its histamine-releasing properties. The data presented here indicate a lack of parallelism between the toxicity of histamine and the toxicity of 48/80 within a single species. It also has been demonstrated recently that, among different species of animals (mice, rats, guinea pigs, and rabbits), the differences in toxicity of 48/80 are small when compared with the differences in toxicity of histamine.[10]

SUMMARY

Mice which have been made highly sensitive to histamine possess only a slightly increased susceptibility to the histamine liberator 48/80.

REFERENCES

1. Dews, P. B., and deBeer, E. J.: Pharmacology of a Polymer With Long Acting Vasodepressor Properties, Federation Proc. **9**: 267, 1950.
2. Feldberg, W., and Paton, W. D. M.: Release of Histamine From Skin and Muscle in the Cat by Opium Alkaloids and Other Histamine Liberators, J. Physiol. **114**: 490, 1951.
3. Paton, W. D. M.: Compound 48/80: A Potent Histamine Liberator, Brit. J. Pharmacol. **6**: 499, 1951.
4. Paton, W. D. M., and Schacter, M.: The Influence of an Antihistamine Drug on the Release of Histamine in the Unanaesthetized Dog, Brit. J. Pharmacol. **6**: 509, 1951.
5. Feinberg, S. M., and Sternberger, L. A.: Action of Histamine Liberator Compound 48/80 in the Guinea Pig, J. ALLERGY **26**: 170, 1955.
6. Miles, A. A.: Increased Permeability of Skin Capillaries Produced by Histamine in Guinea Pigs, J. Physiol. **114**: 35P, 1951.
7. Dews, P. B., Wnuck, A. L., Fanelli, R. B., Light, A. E., Tornaben, J. A., Norton, S., Ellis, C. H., and deBeer, E. J.: The Pharmacology of No. 48-80, a Long-Acting Vasodepressor Drug, J. Pharmacol. & Exper. Therap. **107**: 1, 1953.
8. Parfentjev, I. A., and Goodline, M. A.: Histamine Shock in Mice Sensitized With *Hemophilus pertussis* Vaccine, J. Pharmacol. & Exper. Therap. **92**: 411, 1948.
9. Litchfield, J. T., and Wilcoxon, F.: A Simplified Method of Evaluating Dose-Effect Experiments, J. Pharmacol. & Exper. Therap. **95**: 99, 1949.
10. Loew, E. A., and Papacostas, C. A.: Comparative Toxicity of Histamine and a Histamine-Liberator 48/80, Federation Proc. **14**: 364, 1955.

OBSERVATIONS ON ACACIA AS AN IMMUNIZING, SENSITIZING, ANAPHYLACTOGENIC, AND DESENSITIZING ANTIGEN

HERBERT SILVETTE, PH.D., OSCAR SWINEFORD, JR., M.D., AND LOUISE TULL, B.A.,
CHARLOTTESVILLE, VA.

INTRODUCTION

A SERIES of studies of desensitization with haptens, as contrasted with whole antigens, is in progress in this laboratory. A cheap source of abundant polysaccharide hapten is needed to continue these studies efficiently. The report of Partridge and Morgan[4] suggested that acacia might be such a source. Acacia is cheap, readily available, and widely used commercially. Over 6,800 tons were imported from the Sudan in 1952.[1] It has been shown to be antigenic in rabbits and guinea pigs[2-4] and allergenic in man.[5-7]

Partridge and Morgan[4] reported that treatment of acacia with formamide yielded a polysaccharide which was not antigenic but was haptenic. This non-antigenic acacia derivative caused anaphylactic shock in guinea pigs sensitized passively with antiserum from rabbits immunized with a bacterial protein-formamide-acacia complex. This derivative also precipitated the antiserum, but did not produce antibodies by the immunizing schedule used by them.

Acacia was subjected to a series of screening procedures which are the subject of this report. There were several interesting observations, although the search for a suitable polysaccharide hapten with which to continue the desensitization studies was not successful.

Four different lots of acacia have been investigated—two so-called "bleached white sorts" and two "amber sorts," differing in that the former had been exposed to sunlight to bleach. All four samples yielded positive biuret tests, a pH of 5.0 in 1 per cent aqueous solution, and positive Molisch reactions in dilutions of 1:8,000,000. The nitrogen content was 0.37 per cent in two, 0.35 per cent in one, and 0.36 per cent in the other. These lots were labeled A, B, C, and D, arbitrarily.

Toxicity.—No untoward reactions followed intravenous, intra-abdominal, or subcutaneous injections of 2.0 and 10.0 ml. of 6 per cent solutions of acacia prepared at room temperature and sterilized by Seitz filtration. The pH of such solutions was about 4.5. Maytum and Magath,[2] however, reported peritonitis in guinea pigs unless the acacia solution was buffered to pH 6.6.

Active Sensitization of Guinea Pigs.—Twelve guinea pigs, weighing ±300 grams, were sensitized by single intra-abdominal injections of 600 mg. acacia

From the Allergy Research Laboratory, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Virginia.

This study was made possible by grants from: (1) Eli Lilly and Company, Indianapolis, Ind. (2) Bilhuber-Knoll, Inc., Orange, New Jersey, (3) The National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, Grant No. A-283 (R), and by the donations of generous supplies of acacia by S. B. Penick and Company, New York, New York.

Received for publication Oct. 26, 1954.

(10.0 ml. of 6 per cent solution). One month later they were challenged intravenously with 60 mg. of the sensitizing or of other samples of the gum. Anaphylactic shock, fatal in ten, resulted in every case.

Two other guinea pigs were sensitized by the intra-abdominal injection of 160 mg. acacia-B with Freund's adjuvant (2.0 ml. of an emulsion of 2 parts 20 per cent acacia, 2 parts Bayol-F, 1 part Falba). One month later they were challenged with 60 mg. acacia-B intravenously. Typical anaphylactic death resulted in both.

Active Immunization of Rabbits.—Seventeen albino rabbits, weighing 2.0 to 2.5 kilograms initially, were immunized intravenously with arbitrarily selected doses of 5.0 ml. of 6 per cent acacia solution on three successive days of three successive weeks. Each animal thus received a total of 2,700 mg. acacia. Larger and smaller immunizing doses were not tried. The animals were bled for immune serum five to seven days after the ninth and last injection. Precipitin titers were highest (1:4,000) about five days after the last injection. Precipitins persisted in variable but decreasing titers for six to seven weeks.

In contrast, two rabbits injected subcutaneously with a single 2.0 ml. dose of the acacia-adjuvant mixture described previously (equivalent to 160 mg. of the gum) did not develop precipitins until four to five weeks after injection. The precipitin titers of these animals were lower (1:1,000) than in those immunized intravenously, but persisted for at least three months.

Attempts were made to demonstrate anamnestic responses in four immunized rabbits in which precipitins had disappeared. These were injected with 120 mg. of acacia subcutaneously, followed on two successive days by 300 mg. and 600 mg. intravenously. In one animal the 600 mg. injection caused anaphylactic death. In another, the precipitin titer rose to only 1:200, a very low level. In two others, no return of precipitin was observed seven days after the intravenous injections.

Although no, or very weak, anamnestic responses to three doses of antigen were demonstrated, a second full course of intravenous injections (three weekly for three weeks) reproduced precipitins of the original titers.

Two rabbits initially immunized to acacia-A, when reimmunized with acacia-D, produced sera of equal antiacacia-A and antiacacia-D titers. Similarly, two rabbits initially immunized with acacia-D, and reimmunized with acacia-A, produced sera of equal antiacacia-D and antiacacia-A titers.

Precipitins.—The precipitin reactions were interesting in several respects. For example:

When the antiacacia sera were overlaid with 1:20 to 1:360 dilutions of acacia, a ring formed in a few minutes. It reached a maximum in about one hour at room or incubator temperature.

When the antisera were overlaid with 1:500 to 1:8,000 acacia dilutions, the appearance time of the ring was delayed to thirty minutes or longer in the lower dilutions, reaching maximum intensity and titer in two to four hours. The rings diffused on standing at room or refrigerator temperature. In the stronger concentrations (1:20, 1:40) the rings diffused downward. In the weaker dilutions diffusion occurred both up and down.

Mixing the contents of the precipitin tubes yielded no sediment, although the mixtures became hazy. Attempts to obtain some precipitate by varying the proportions of antigen and antibody, the time and temperature of incubation, and the speed of centrifugation were unsuccessful.

The titers of cross precipitin reactions with A, B, and D antiacacia rabbit sera using acacia-A, -B, -C, and -D as precipitating antigens were quite uniform. The two-hour (maximum) readings varied from 1:1,000 to 1:4,000. Direct titers were no higher than the cross-tests.

Occasionally, sera from normal rabbits gave slight ring tests with strong (1:20 to 1:100) acacia solutions; 1:400 and weaker acacia dilutions gave negative ring tests with normal rabbit serum. To test the specificity of these rings, several guinea pigs were given 3 to 5 ml. of the normal rabbit serum intra-abdominally. The next day they were challenged with 60 mg. of acacia intravenously. None showed anaphylaxis.

Acacia-A and -B, 1:80 to 1:100, gave occasional transient positive ring tests with Types II and VIII antipneumococcal rabbit serum but not in weaker acacia dilutions. Other acacia samples were not tested. However, Type II pneumococcal polysaccharide (1:1,000) did not precipitate antiacacia rabbit serum, in agreement with Partridge and Morgan.[4]

No precipitins were demonstrated in sera from guinea pigs which had been actively sensitized with acacia, although these same sera passively sensitized other guinea pigs readily.

Arthus Type Reactions.—Two-tenths milliliter of 6 per cent acacia was injected intracutaneously into four immunized rabbits with antiacacia precipitin titers of 1:4,000 to 1:8,000. The reactions were negligible the first day. On the second and third days the test sites were erythematous and palpably indurated in an area about 1.0 cm. in diameter with no central necrosis. The skins looked and felt normal in seventy-two to ninety-six hours.

In two other rabbits there was severe necrosis at seventy-two hours, although the diameter of the reaction was only 1.0 cm. and there was little surrounding erythema.

None of the rabbits immunized with acacia plus adjuvant gave definitely positive delayed skin reactions.

The flanks of two other rabbits were injected intracutaneously with 0.2 ml. of each of the following solutions of acacia: 0.1 per cent, 0.3 per cent, 0.6 per cent, 1.0 per cent, 3.0 per cent, 6.0 per cent and 20 per cent. The initial precipitin titers were 1:1,000 to 1:2,000. Small wheals appeared at all sites within about forty minutes and persisted for about twenty-four hours. The outlines were slightly irregular, but there was no central pallor or peripheral flare. The reactions were uniformly pink and slightly swollen. At forty-eight hours all the reactions had subsided except at the 6 per cent and 20 per cent sites. The 6 per cent sites were graded 2+ in one and 3+ in the other, and the 20 per cent sites were graded 3+ in one and 1+ in the other (1+ = firm, erythematous area, ±1.0 cm. diameter; 2+ = like 1+ with slight central necrosis; 3+ = central 1.0 cm. firm nodule with extreme central necrosis). At five days there was a small pea-sized lump at each of these sites.

Desensitization Against Arthus Type Reactions.—The last two rabbits just described were given a preliminary subcutaneous dose of 2.5 ml. (150 mg.) of 6 per cent acacia, followed by 2.0 ml., 5.0 ml., and 5.0 ml. intravenously within two days. The precipitin titer the next day had not changed in one, but had increased from 1:2,000 to 1:8,000 in the other. On that same day they were given 0.2 ml. of 6 per cent acacia intracutaneously. The Arthus reactions were essentially unchanged (2+) forty-eight hours later.

Six days after the last previous intravenous doses, the rabbits were given 5.0 ml. (300 mg.) intravenously twice daily for three days. The immediate skin reactions the day after the last dose were weakly positive. The delayed reactions were 1+ at twenty-four hours. The precipitin titer then was 1:2,000 in one and 1:4,000 in the other.

Four days after the last preceding intravenous injections, the rabbits were given 2.5 ml. of 6 per cent acacia subcutaneously in the morning and 5.0 ml. intravenously in the afternoon. They were given 10.0 ml. (600 mg.) of 6 per cent acacia intravenously twice daily for the next two days. The immediate reactions two days later were faint; the forty-eight-hour reactions were negative in both. The precipitin titer was 1:1,000 in one rabbit and 1:4,000 in the other. The next day the Arthus type response was still negative. The animals were considered desensitized at this point. In these two desensitized animals the precipitin titer in one was the same as at the beginning of the experiment. In the other the titer had risen slightly, from 1:2,000 to 1:4,000. It is of interest that so much antigen was required to desensitize. No effort was made to determine the duration of this desensitization. More study should be given to this problem.

Heterologous Passive Sensitization.—Twenty-nine guinea pigs were sensitized with 1.0 ml. antiacacia-A, -B, or -D rabbit sera, intra-abdominally, with precipitin titers of 1:2,000 to 1:4,000. The next day the animals were challenged with 60 mg. acacia-A, -B, -C, or -D intravenously. All the pigs reacted by anaphylactic death when challenged with either the specific or the other samples of acacia.

Sensitizing doses of antiacacia-A rabbit serum were titrated against shocking doses of acacia-A and acacia-C solutions in thirty-one pigs. Definite anaphylaxis was produced by as little as 0.1 to 0.2 ml. of antiserum and 2.0 to 3.0 mg. of antigen. However, the smallest combinations which regularly produced fatal or severe anaphylaxis were 0.2 and 0.33 ml. antiserum with 6.0 mg. of antigen. Larger doses of antigen, with 0.33 ml. antiserum, invariably caused fatal shock. Again crossed antigen-antibody systems were as effective as the direct ones. Antisera with lower precipitin titers (1:200) required 1.0 to 2.0 ml. for passive sensitization.

Duration of Heterologous Passive Sensitization.—Four guinea pigs were sensitized passively with 0.33 ml. of antiacacia-A rabbit serum. They were challenged with 60 mg. of acacia intravenously, one on the seventh, two on the tenth, and one on the fourteenth day. The reactions were: anaphylactic death in one on the seventh day; moderate anaphylaxis with prompt recovery in two on the tenth day; and an equivocal reaction in the fourth animal on the four-

teenth day. These are in accord with earlier observations[11] that anaphylactic reactions were obtained irregularly after ten days and not at all after thirteen days in guinea pigs sensitized passively with heterologous antiserum. The role of larger amounts of sensitizing antibody in prolonging passive sensitization was not studied.

Homologous Passive Sensitization.—One guinea pig was sensitized passively with 1.0 ml. of antiacacia guinea pig serum intra-abdominally. Moderately severe shock occurred when challenged with 60 mg. acacia intravenously the next day. Two other animals, sensitized with 3.0 ml. antiacacia guinea pig serum, had fatal anaphylaxis when challenged the next day.

The antiserum was obtained from guinea pigs which had been given a single intra-abdominal injection of 10.0 ml. of 6 per cent acacia twenty-one days before.

Heat-Treated Acacia.—A 20 per cent solution of acacia-B, heated in a water bath at 96° C. for six hours, was diluted to make a 6 per cent solution. Two rabbits were immunized with this heated acacia by the schedule described (5.0 ml. of 6 per cent solution intravenously for three successive days of three successive weeks). Both animals produced immune serum which passively sensitized to and gave precipitin reactions with the heated acacia and with all four samples of native acacia.

Two other rabbits were immunized with acacia-A which had been heated at 100° C. for two hours in a drying oven. This dry-heated acacia was also antigenic, producing precipitating and sensitizing antiserum specific for both heated and native acacia.

Formamide-Treated Acacia.—Acacia-A and -B were each treated by the formamide method of Partridge and Morgan.[4] No difference could be established between the A and B samples so treated. This formamide-treated acacia contained 0.28 per cent N, compared (1) to 0.24 per cent N as reported by Partridge and Morgan and (2) to 0.35 to 0.37 per cent N of the native gum. When the immunizing schedule of these authors[4] was used in two rabbits (3×0.5 mg. intravenously; one week's rest; 3×0.5 mg. intravenously), neither precipitins nor sensitizing antibodies could be demonstrated, in agreement with Partridge and Morgan.[4]

However, when three rabbits were immunized with formamide-treated acacia by the schedule used with the native gum (3×300 mg.; four days' rest; 3×300 mg.; four days' rest; 3×300 mg.), potent immune sera, comparable to those from whole acacia, were obtained from each animal. Guinea pigs passively sensitized with such rabbit antisera developed fatal anaphylactic shock when challenged with formamide-treated, heat-treated, or native acacia.

Formamide-treated acacia proved less anaphylactogenic than the native gum. The minimal fatal shocking dose of formamide-treated acacia observed in twelve pigs sensitized with 0.33 ml. antiacacia-A rabbit serum was about five times (30 mg.) that of the native gum. Sixty milligrams, or ten times the fatal challenging dose of whole acacia, killed only one of three pigs.

Formamide-treated acacia was highly reactive chemically (see discussion).

Unsuccessful Attempts to Extract a Polysaccharide Hapten from Acacia.—Since the formamide treatment of acacia by the method of Partridge and Morgan[4] resulted in a material which was antigenic and highly reactive chemically, and therefore unsatisfactory, five other methods were used to attempt to extract a polysaccharide hapten. None of the polysaccharides obtained by these methods retained their immunologic specificity and, therefore, they were not the desired haptens. Because of this, only brief outlines of the methods employed are given:

(a) Acacia, made acid with hydrochloric acid at pH 1 and 3.5, and with acetic acid at pH 4 and 6, was heated in the water bath for two hours. The polysaccharides were then precipitated with alcohol. Abundant yields of polysaccharide were obtained at pH 3.5 and 4.0.

(b) Acacia was heated with 8 per cent sodium hydroxide plus 8 per cent sodium acetate in the Arnold sterilizer, then adjusted to pH 6 with hydrochloric acid and precipitated with alcohol.

(c) The method of Heidelberger, Avery, and Goebel,[9] which consists of treating with strong hydrochloric acid at room temperature, precipitation by alcohol, and purification by successive treatments with acetone, sodium nitrite, and acetic acid, was tried.

(d) The method of Campbell[12] for extracting an antigenic polysaccharide from ascaris was applied to acacia. This consists essentially of treatment with sodium hydroxide and ether at pH 8, followed by treatment with trichloroacetic, phosphotungstic and sulphuric acids with repeated alcohol precipitation.

(e) The Myrvik[14] method for extracting polysaccharide from tubercle bacilli was also tried. This consisted of heating acacia with 4 per cent sodium acetate and 8 per cent sodium hydroxide and precipitating from the alkaline solution with alcohol. This was purified by repeated precipitation with alcohol from a pH of 8.0.

All these gave positive Molisch reactions in dilutions of 1:1,000,000 or more. None gave specific precipitin tests with antiacacia rabbit serum, although several gave nonspecific ring tests with normal and with immune sera. None caused dyspnea or anaphylaxis when used to challenge by aerosol or intravenous injection, although the animals reacted subsequently to challenges with whole acacia by aerosol and by vein.

The search for a polysaccharide hapten from acacia has been abandoned, for the present at least.

Desensitization.—Six guinea pigs were passively sensitized with 0.33 ml. antiacacia-A rabbit serum intra-abdominally. Two of them served as controls. Another pair received six desensitizing intra-abdominal injections of gradually increasing amounts (15, 30, 45, 60, and 150 mg.) of acacia-A during the succeeding two days. The remaining two guinea pigs were given similar desensitizing doses of formamide-treated acacia. No anaphylactic or other untoward symptoms were observed from the intra-abdominal desensitizing injections (large as they were in comparison with the intravenous shocking doses). Twenty-four

hours after the final desensitizing injection, the animals desensitized with the acacia-A were challenged intravenously with 120 mg. acacia-A (twenty times the usual lethal dose). The animals desensitized with formamide-treated acacia were challenged with 60 mg. of it intravenously. No anaphylactic or other symptoms were observed, while control animals were fatally shocked by smaller doses of the respective antigens.

Five days later, the two guinea pigs desensitized with acacia-A were re-challenged with 60 mg. acacia-A intracardially, again with negative reactions, showing persistence of desensitization for at least six days.

A marked increase in tolerance, but not complete desensitization, followed sublethal anaphylactic reactions to small intravenous doses of acacia in four animals.

Aerosol Experiments.—Seventeen guinea pigs, passively sensitized with antiacacia rabbit serum, were exposed in a glass box to 3 per cent or to 6 per cent acacia aerosol fog. Twelve developed moderate to severe dyspnea in three to nine minutes. Normal pigs are not affected by acacia aerosols.

Aerosol Desensitization.—Ten of the passively sensitized pigs that reacted were left in the fog for from ten to eighty-five minutes. The dyspnea gradually lessened and finally disappeared. When these ten animals were re-exposed to acacia aerosol after intervals ranging from ten minutes to several days, nine showed no dyspnea. The tenth pig, after an initial aerosol exposure of ten minutes, developed moderate dyspnea on re-exposure. This pig and the two others which had been removed from the fog when their initial reactions began were desensitized by several short aerosol re-exposures.

So far, fatal or even severe anaphylactic shock has not been produced in actively or passively sensitized pigs by the inhalation of acacia fog. This is in contrast to (1) the occasional rapid anaphylactic death of guinea pigs sensitized with antipneumococcal rabbit serum when exposed to aerosol of the type-specific polysaccharide,[13] and (2) the frequent anaphylactic death from specific aerosols in congenitally sensitive pigs.

Seventeen actively sensitized pigs were desensitized locally by exposures to 3 per cent acacia aerosol. Desensitization time was much longer than for passively sensitized pigs. Specifically, three took from one to two hours, eight took from two to three hours, two took from four to five hours, three took from seven to nine hours, and one took eleven hours. The average was three and three-tenths hours, compared with an average of less than one hour for the passively sensitized group. This difference has been observed with other antigen-antibody systems also.

Active local sensitization by inhalation of an aerosol of whole acacia was attempted unsuccessfully. Six guinea pigs were exposed to an aerosol of 3 per cent acacia for one hour daily, five days each week for three weeks. This was repeated three weeks later and again five weeks later. They did not react to an aerosol of 6 per cent acacia when challenged before the second and third or after the third series of aerosol exposures. The conclusion is obvious that active sensitization by inhalation sufficient to cause reactions to an aerosol of

whole acacia is not readily produced. Perhaps other schedules of aerosol exposures would be successful.[10] Through an oversight, the animals were not challenged intravenously to see if systemic sensitization had been produced.

Congenital Sensitization to Acacia.—Nineteen guinea pigs, born of mothers actively sensitized to acacia, were challenged with 3 per cent acacia aerosol. Fifteen were challenged three weeks after birth. There were three prompt anaphylactic deaths, plus two severe, three moderate, and two slight-moderate reactions and one slight reaction. Four of the pigs did not react to the aerosol. The aerosol exposure of those that reacted by anaphylactic death was less than three minutes. The others reacted in less than five minutes in the fog.

Four pigs were challenged when they were 3 days old. All four reacted moderatedly to a thirty-second exposure to the aerosol. When they were 6 weeks old, they were rechallenged. There was one anaphylactic death, plus one slight-moderate and two moderate reactions.

The anaphylactic deaths were in sharp contrast to the failure to elicit fatal reactions in pigs that had been actively or passively sensitized directly. Pigs congenitally sensitive to rabbit serum were also highly reactive to aerosols. The reactions were specific, that is, they did not react to aerosols of saline or of pneumococcal polysaccharides. Nor do normal newborn pigs react to acacia aerosols.

DISCUSSION

No demonstrable chemical or immunologic differences between the four lots of acacia were found in these limited experiments. It seems evident that the antigenicity of acacia is inherent in the gum and is not due to contaminants.

Although the chief reason for this study—the search for a polysaccharide hapten from acacia—was not successful, a number of interesting observations were made. Examples are: the atypical anamnestic, precipitin, and Arthus reactions; the persistence of precipitin titers when the Arthus reactions seemed suppressed by desensitizing procedures; the marked chemical reactivity of the formamide-treated acacia; the difference between aerosol desensitization times of actively and passively sensitized pigs; and the high incidence of anaphylactic death from acacia aerosol in congenitally sensitive pigs.

The demonstrated antigenicity of the formamide-treated acacia was disappointing but not surprising, since the nitrogen content was reduced only from 0.36 in whole acacia to 0.28 per cent by the formamide treatment. Some unexpected observations on formamide-treated acacia have compensated, in part, for the failure to find the hapten. For example: formamide-treated acacia is quite active chemically, as demonstrated by its striking ability to precipitate gamma globulin from serum promptly. This should be studied further elsewhere, since this laboratory is not equipped to pursue this interesting and potentially useful observation.

The formamide-treated acacia is a weaker and more unpredictable anaphylactogen than acacia, although it readily produces precipitins and sensitizing antibodies in good titer. When several guinea pigs were sensitized passively and divided into two groups, the first group reacted anaphylactically when challenged

intravenously with whole acacia. Reactions in the other group, challenged with the same dose of formamide-treated acacia, showed either very slight or fatal anaphylaxis, quite unaccountably. It is conjectured that nonantibody globulins of the recipients' plasma combined with the chemically active formamide-acacia sufficiently to neutralize the amount of available antigen necessary to produce anaphylaxis.

Several of the polysaccharides obtained by acid or alkali treatment of acacia gave nonspecific ring precipitin tests with normal guinea pig and rabbit sera. Several others were inert when overlaid on or mixed with specific and nonspecific antisera. None retained the immunologic specificity of acacia. Whereas the search for a specific polysaccharide hapten in acacia has been abandoned, at least temporarily, this does not mean that a hapten may not be extracted from acacia eventually.

The Arthus experiments were interesting in several respects, namely: (1) The small area of skin involved in the reaction, even when necrosis was observed; (2) the negligible effect of the large desensitizing doses of acacia on the precipitin titers; (3) the large amount of desensitizing acacia necessary to suppress the Arthus reactions; and (4) inability to obtain sedimented precipitates from antigen-antibody mixtures prevented quantitative studies of the amount of antigen necessary to neutralize precipitin in vivo or in vitro. If these observations can be repeated and extended, a re-examination of the apparently established role of precipitin in the Arthus reaction would seem in order.

The poor anamnestic response to a short course of reinjections of acacia after precipitins had disappeared was unexpected and difficult to explain in the face of the good precipitin response to a subsequent full immunizing course of acacia.

The aerosol experiments are presented in summary form, as more detailed studies and discussions have been reported.[13] Others are in progress.

SUMMARY

Four different lots of gum acacia were found to be equally effective as immunizing, sensitizing, anaphylactogenic, and desensitizing antigens, as shown by cross-precipitin tests and cross-anaphylaxis experiments.

The antigenicity of acacia is considered to be a property of the native substance, and not due to a contaminant or impurity.

Rabbits were readily immunized with, and guinea pigs actively sensitized to, acacia.

Antiacacia rabbit serum in small doses passively sensitized guinea pigs. They reacted to intravenous and aerosol challenges with acacia. This sensitization lasted about thirteen days.

Homologous antiacacia serum also passively sensitized guinea pigs, but none of these pigs has reacted, so far, to an aerosol challenge with acacia. The duration of passive sensitization with homologous serum was not studied.

Precipitins persisted in rabbits for six to seven weeks after intravenous immunization, and for three months after a single subcutaneous injection of acacia with Freund's adjuvant.

Precipitin behavior was bizarre in that precipitates could not be collected by centrifugation, although specific ring tests were obtained with ease.

Passively sensitized guinea pigs were effectively desensitized by intra-abdominal injections of acacia.

Exposure to acacia aerosol produced dyspnea in a high percentage of actively, passively, and congenitally sensitized animals.

Continued or repeated aerosol exposure produced local desensitization readily in passively sensitized guinea pigs. Desensitization of actively sensitized pigs took much longer.

Arthus type reactions to intracutaneous injections of acacia in immunized rabbits were obtained in varying degree. Desensitization against this type of reaction followed intravenous injections of several large doses of acacia.

Formamide-treated acacia had a lower nitrogen content than the native gum, but was still antigenic, although its anaphylactogenic and precipitating powers seemed to be reduced. Formamide-treated acacia precipitated globulin (chiefly gamma, by crude tests) from normal and immune guinea pig and rabbit serum.

Heating the acacia did not appreciably affect its specificity or immunizing properties.

Treatment of acacia by several methods, using acid or alkali with and without heat, failed to yield a haptenic polysaccharide, although nonhaptenic polysaccharides which had lost their immunologic specificity were obtained readily.

REFERENCES

1. S. B. Penick and Company, New York: Personal communication.
2. Maytum, C. K., and Magath, T. B.: Sensitivity to Acacia, J. A. M. A. **99**: 2251, 1932.
3. a. Uhlenhuth, P., and Remy, E.: Zur Frage der Antikörper gegen Kohlenhydrate (Gummi arabicum), Ztschr. Immunitätsforch. u. exper. Therap. **79**: 318, 1933.
   b. Uhlenhuth, P., and Remy, E.: Zur Frage der Antikörper gegen Kohlenhydrate; Versuche mit Glukose, Glukosamin, Amygdalin, Cathartinsäure und einem an Stickstoff abgebauten Gummi-arabicum-Präparate, Ztschr. Immunitätsforch. u. exper. Therap. **82**: 229, 1934.
4. Partridge, S. M., and Morgan, W. T. J.: Artificial Antigens With Agar, Gum Acacia and Cherry Gum Specificity, Brit. J. Exper. Path. **23**: 84, 1942.
5. Bohner, C. B., Sheldon, J. M., and Trenis, J. W.: Sensitivity to Gum Acacia, With a Report of Ten Cases of Asthma in Printers, J. ALLERGY **12**: 290, 1941.
6. Spielman, A. B., and Baldwin, H.: Atopy to Gum Arabic, J. ALLERGY **4**: 451, 1933.
7. Seidman, R. M.: Cutaneous Reactivity of Guinea Pigs to Gum-Arabic, J. Immunol. **38**: 237, 1940.
8. a. Gelfand, H. H.: The Allergic Properties of the Vegetable Gums, J. ALLERGY **14**: 203, 1943.
   b. Gelfand, H. H.: The Vegetable Gums by Ingestion in the Etiology of Allergic Disorders, J. ALLERGY **20**: 311, 1949.
9. Heidelberger, M., Avery, O. T., and Goebel, W. F.: A "Soluble Specific Substance" Derived From Gum Arabic, J. Exper. Med. **49**: 847, 1929.
10. Ratner, B.: The Temporal and Quantitative Factors Influencing the Development of Experimental Asthma in the Guinea Pig, J. ALLERGY **24**: 316, 1953.
11. Swineford, O., and Reynolds, R. J.: Studies in Bacterial Allergy. V. Persistence of Desensitization, With Bacterial Haptens, of Guinea Pigs Sensitized Passively With Heterologous Serum, J. ALLERGY **22**: 350, 1951.
12. Campbell, D. H.: An Antigenic Polysaccharide Fraction of Ascaris Lumbricoides (From Hog), J. Infect. Dis. **59**: 266, 1936.
13. a. Swineford, O.: Studies in Bacterial Allergy. VI. Hapten Aerosol Desensitization of Guinea Pigs Passively Sensitized to Specific Pneumococcal Polysaccharides, J. ALLERGY **25**: 260, 1954.
    b. Swineford, O., Tull, L. N., and Westervelt, F. B.: Studies in Bacterial Allergy. VII. Bronchial Desensitization and Resensitization in Passively Sensitized Guinea Pigs, J. ALLERGY **26**: 157, 1955.
14. Myrvik, Q. N.: Personal communication.

SERUM ELECTROPHORETIC PATTERN IN EXPERIMENTAL HYPERSENSITIVITY

LEO H. CRIEP, M.D., A. I. SCHEPARTZ, PH.D., MACY I. LEVINE, M.D., AND ROBERT S. TOTTEN, M.D., PITTSBURGH, PA.

THE allergist is interested in the subject of collagen disease because its pathologic lesions closely resemble those produced in experimental hypersensitivity and also because some of the clinical conditions grouped under this heading are of allergic etiology.[1-12] Exception, however, is taken by some to the view that fibrinoid degeneration is in the nature of an immune response.[13-18] Because of this, and also because of suggestive clinical speculation as to the role played by bacterial allergy in collagen disease,[19-24] we demonstrated, in 1949, the immunologic nature of these lesions in rabbits sensitized with streptococcus toxin.[25] Furthermore, we also showed that interference with the antibody-forming tissues by suitable x-radiation reduces to a marked degree the extent, frequency, and severity of the allergic vascular response and of carditis in rabbits.[26] Similar inhibiting effects are produced by the administration of nitrogen mustard to animals sensitized in this manner.[27, 28] As a further link in the evidence of the immunologic character of this condition, we also produced experimental arteritis by passive sensitization to horse serum[29] and showed that adrenalectomy enhances the development of the lesions.[30] Such evidence is offered in support of the immunologic character of this condition.

In line, therefore, with present available information, and because electrophoretic pattern changes are reported in instances of immune response,[31-34] in lupus erythematosus disseminatus,[35, 36] and to a lesser extent in periarteritis nodosa,[37] we became interested in discovering whether any changes could be observed in the serum electrophoretic pattern of sensitized rabbits. We therefore undertook the study which forms the basis for this article. Patterns thus obtained are correlated with quantitative antibody determinations in the same sera and pathologic studies of the tissues. The second part of the article deals with a study which was similar except for the fact that the animals were treated with cortisone immediately after the administration of the sensitizing dose of antigen.

MATERIALS AND TECHNIQUE

Male albino rabbits, weighing approximately 2 kg., were used throughout these experiments. Animals were housed in an air-conditioned room and were fed lettuce, carrots, and Purina Rabbit Checkers.

From the Allergy Research Laboratory, School of Medicine, University of Pittsburgh, at the Montefiore Hospital, and the U. S. Veterans Hospital, Pittsburgh, Pennsylvania.

Supported in part by a grant from the Lasden Foundation, Nepera Park, Yonkers, New York.

Presented at the eleventh annual meeting of the American Academy of Allergy, Feb. 7 to 9, 1955, Hotel Statler, New York, N. Y.

Received for publication Feb. 9, 1955.

The technique of sensitization and of cortisone administration was essentially that employed by Germuth[38] in his experiments. Crystalline bovine plasma albumin (Armour Laboratories) was dissolved in 0.9 per cent saline solution to form a 10 per cent solution, and solid sodium bicarbonate was added to give a pH of 7.4. Solutions were freshly prepared prior to use. Cortisone acetate (Merck & Company, Inc.), in saline suspension containing 25 mg. per millimeter, was administered intramuscularly in the upper portion of the hind legs. Blood samples were obtained from the marginal ear vein of every rabbit at the beginning and conclusion of each experiment. These samples were allowed to clot in a refrigerator overnight and then the sera were removed by centrifugation. Serum samples were transferred to sterile vials and stored, frozen, at –15° C. until used. Samples for electrophoresis were diluted 1:3 and dialyzed for at least four hours against a sodium barbital buffer at pH 8.6 and ionic strength 0.1 in a continuously stirring unit. Electrophoretic analyses were carried out in an Aminco-Stern apparatus at 1.6° C. in an electric field of 5.7 volts per centimeter for 120 minutes, using the barbital buffer just described. Patterns for the descending boundaries were enlarged and the areas of the components were determined by planimetry. The area of each component was compared with the total area of the pattern and was recorded as a percentage of the total area. A representative number of sera were analyzed for total nitrogen by the micro Kjeldahl method. Quantitative antibody-nitrogen determinations were performed according to the technique of Kabat and Mayer.[31] Animals were sacrificed by the suboccipital injection of 20 ml. of air in the first experiment and by chloroform anesthesia in the second experiment. All animals were autopsied, tissues were placed in 10 per cent Formalin, and histologic sections of heart (one through the base including the root of the aorta and generally the coronary artery and aortic valve, and one horizontally through the ventricles), lungs, liver, spleen, adrenals, kidneys, and diaphragm were studied, using the routine hematoxylin and eosin stain.

EXPERIMENT I. ELECTROPHORETIC, TOTAL NITROGEN, QUANTITATIVE ANTIBODY, AND PATHOLOGY CHANGES IN EXPERIMENTAL HYPERSENSITIVITY

On the first day of the experiment, two rabbits serving as controls each received 5 ml. of sterile isotonic saline in the marginal ear vein, and in the same manner, fourteen rabbits were given bovine plasma albumin intravenously in a dosage of 250 mg. per kilogram body weight. All animals appeared to be in good condition until the time of sacrifice fourteen days after the initial injection. Serum samples obtained prior to sensitization and just prior to sacrifice were analyzed electrophoretically, for quantitative antibody content and for total nitrogen.

Results.—

A. *Electrophoretic data:* Electrophoretic analyses were performed on the sera of the two controls and on eleven of the fourteen experimental animals in the series. The three remaining sera were not studied electrophoretically because of technical difficulties. The results of these analyses are given in Table I,

which lists the relative percentages of serum protein components found in the animals before and after sensitization. The values obtained prior to sensitization were compared with data obtained from a series of fourteen normal rabbits run previously* and showed no significant differences. Hence, all animals were judged to be initially "normal" rabbits. The patterns obtained on the two control animals showed no significant changes fourteen days after injection with normal saline. The solid line in Fig. 1 illustrates the electrophoretic pattern of a normal rabbit prior to sensitization. It shows the various protein components. The broken line in this illustration typifies the patterns obtained on sera fourteen days after sensitization. Since it may be noted in Table I that individual variations occur in the sera of the rabbits, it was necessary to analyze all the electrophoretic data on a statistical basis. The arithmetic means, standard error of means, standard deviations, and other necessary statistical values were calculated for all groups of samples. All comparisons to which groups of data were subjected were submitted to "t" tests for significance of correlation. If a given change in pattern component was found to be significant at the 1 per cent

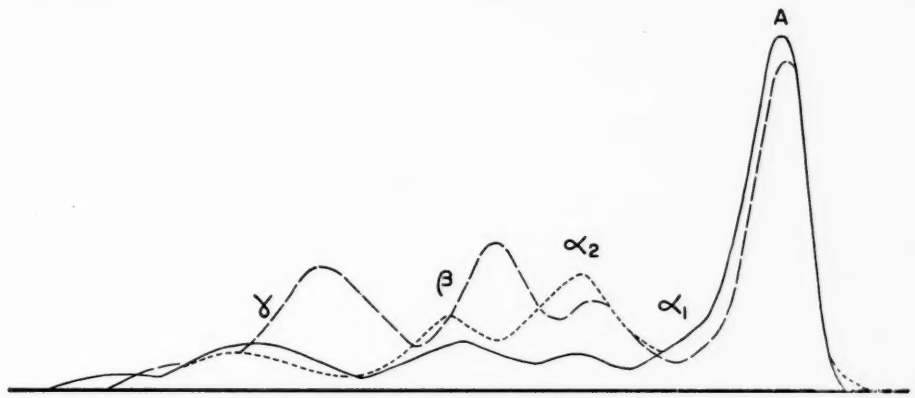


Fig. 1.—Superimposition of typical electrophoretic patterns.
Solid line: normal pattern.
Broken line: fourteen days after sensitization.
Dotted line: sensitized and cortisone-treated.
A, Albumin; α_1, alpha$_1$ globulin; α_2, alpha$_2$ globulin; β, beta globulin; γ, gamma globulin.

level (only one possibility in 100 that the given change could occur by chance), it was considered to be "highly significant." If it was found to be at the 2 per cent level, it was considered "significant," while if at the 5 per cent level it was considered to have "a tendency toward significance." Lower levels of significance were judged unacceptable. Upon examination of the data in this experiment, we find that several changes have taken place in the serum patterns of rabbits fourteen days following initial administration of antigen. Statistically, we find a decrease in albumin, an increase in γ globulin, and an accompanying decrease in A/G ratio, all being highly significant. The decrease in α_1 globulin was found to be significant. Other changes which might

*The mean percentages for normal rabbits were found to be: A, 59.9 ± 1.64; α_1, 4.4 ± 0.27; α_2, 8.5 ± 0.72; β, 14.2 ± 0.89; γ, 12.9 ± 1.35; A/G, 1.55 ± 0.11 (Schepartz, A. I.; Unpublished results.)

TABLE I. ANALYSES OF SERA BEFORE AND AFTER SENSITIZATION IN EXPERIMENT I

RABBIT NUMBER	RELATIVE PERCENTAGES										A/G		TOTAL PROTEIN (GM. PER CENT)		ANTIBODY-N (MG.N/ML.)
	A		α_1		α_2		β		γ						
	b	a	b	a	b	a	b	a	b	a	b	a	b	a	a
203	58.8	52.8	5.2	2.6	7.9	7.5	17.7	19.3	10.4	17.9	1.42	1.11			0.0
204	67.4	32.9	3.6	2.0	8.6	17.8	17.2	34.2	3.2	13.1	2.07	0.49	5.0	5.1	0.0
205	47.2	39.3	3.8	1.4	13.2	17.4	17.9	20.2	17.9	21.9	0.89	0.65	6.5	6.3	trace
206	48.4	39.4	4.0	4.8	10.1	11.3	12.9	17.3	24.6	27.2	0.94	0.44	6.4	9.7	0.040
207	53.8	55.5	5.5	7.1	8.4	7.1	20.1	16.4	12.2	13.9	1.16	1.25			0.0
208	65.0	50.6	3.5	4.9	5.7	15.7	20.4	12.0	5.3	16.8	1.87	1.02	5.4	5.6	trace
210	51.8	54.9	4.6	3.5	13.3	9.3	18.3	14.4	12.0	17.9	1.08	1.22	8.4	7.2	0.0
212	53.3	47.2	3.5	2.9	11.1	14.3	15.9	17.6	16.2	18.0	1.24	0.89			trace
214	60.6	54.9	6.8	1.7	8.8	4.8	15.9	17.4	8.0	21.3	1.54	1.21	6.1	6.6	0.0
215	45.7	36.9	5.3	1.5	17.7	12.4	16.0	22.6	15.3	26.7	0.85	0.58	7.6	7.0	0.038
216	55.0	30.1	11.5	1.7	10.8	26.0	12.9	26.9	9.8	15.3	1.22	0.43	5.3	7.2	0.0
Mean	55.2	45.0	5.2	3.1	10.5	13.1	16.8	19.9	12.3	19.1	1.30	0.85			
Standard error of the mean	2.14	2.70	0.70	0.55	0.99	1.83	0.74	1.86	1.83	1.43	0.12	0.10			
Controls															
201	58.0	60.9	2.8	2.8	9.1	6.7	22.5	16.6	7.5	13.0	1.38	1.56	5.0	6.2	0.0
202	49.6	58.3	2.5	2.7	10.6	7.7	18.0	15.7	19.3	15.7	0.99	1.40	6.0	5.0	0.0

Key to Symbols

b, Before
a, After
A, Albumin
α_1, Alpha$_1$ globulin
α_2, Alpha$_2$ globulin
β, Beta globulin
γ, Gamma globulin
A/G, Albumin/ total globulin

have seemed apparent were found to have no significance. A representative number of sera (including sera showing high γ globulin or high antibody content) were analyzed by the Kjeldahl method for total nitrogen. Values obtained in this way were converted to total protein figures and the results are given in Table I. The total protein studies of these sera were done in order to determine whether increases in any components caused increases in total protein, or whether the increases in some of the components were at the expense of other constituents. These data indicate no significant trends or changes other than the minor variations in blood protein usually noted in rabbits.

B. *Quantitative antibody-N determinations:* These were carried out on rabbit sera fourteen days following sensitization with bovine plasma albumin. The results as seen in Table I indicate that two rabbits showed appreciable antibody-N quantities and three showed traces of antibody-N at the time of sacrifice.

C. *Pathology:* Lesions were found in the locations and in the frequency listed in Table II. The changes were similar to those described by Germuth[38] in animals sacrificed on the fourteenth day after the injection of antigen. The changes may be conveniently grouped as follows:

Cardiovascular System: (a) Subintimal infiltration. This consisted of a linear or focal infiltration of inflammatory cells immediately beneath the intima

TABLE II. SUMMARY OF ANATOMIC FINDINGS IN EXPERIMENT I. TISSUES EXAMINED FOURTEEN DAYS AFTER SENSITIZATION

ANIMAL NUMBER	SUBENDOTHELIAL INFILTRATION	ARTERITIS	VALVE LESIONS	FOCAL MYOCARDITIS	GLOMERULONEPHRITIS	SPLEEN HYPERPLASIA
201	0	0	0	0	0	0
202	0	0	0	0	0	0
203	0	0	0	1+	0	0
204	4+	4+	4+	0	3+	4+
205	0	0	0	1+	4+	4+
206	4+	0	4+	3+	2+	4+
207	2+	0	0	0	0	1+
208	1+	0	1+	0	0	2+
209	0	0	1+	0	0	2+
210	4+	3+	–	0	1+	4+
211	0	0	0	0	0	1+
212	1+	4+	3+	0	3+	4+
213	0	0	1+	0	0	3+
214	0	0	3+	0	0	3+
215	1+	0	2+	0	0	3+
216	1+	0	4+	0	4+	4+
	57%	22%	71%	22%	44%	93%

0 = Negative
– = Not examined
Animals 201 and 202 are controls. This information was not made available at the time of the tissue examination.

of large blood vessels, chiefly the ascending aorta and pulmonary artery (Fig. 2, A). The cellular exudate consisted of lymphocytes and larger mononuclear cells, as well as occasional polymorphonuclear leukocytes. There was usually edema of the adjacent intima, occasionally extending into the media. (b) Valvulitis. The same reaction was seen in the aortic and, rarely, in the mitral valve cusps (Fig. 2, *B*). In addition to the exudate just described, there were occasional small areas which resembled fibrinoid necrosis. (c) Myocarditis. In

three animals, a focal myocarditis was observed, two consisting merely of small collections of lymphocytes. However, this finding is not uncommon in normal rabbits. In the third animal, there were necrosis of muscle bundles and an exudate of lymphocytes, as well as larger mononuclear cells. (d) Arteritis.

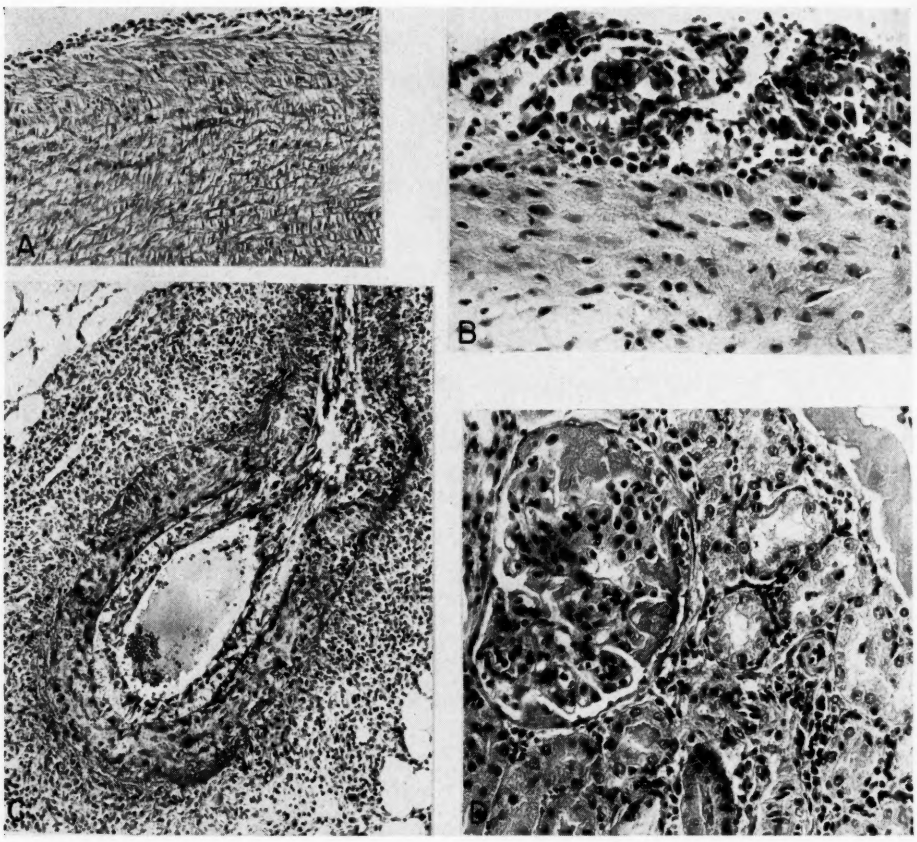


Fig. 2.—Histologic Sections.—
A, Rabbit 204. Aorta. Linear intimal infiltration of lymphocytes and larger mononuclears, as well as proliferation of the endothelial cells. (Magnification, ×140; reduced 3/10.)
B, Rabbit 214. Aortic valve showing details of the mononuclear exudate. (Magnification, ×280; reduced 3/10.)
C, Rabbit 204. Coronary artery showing panarteritis. Note marked edema of the intima and fibrinoid change in the media. (Magnification, ×140; reduced 3/10.)
D, Rabbit 216. Kidney showing proliferation of cells in the glomerular tuft, protein precipitate in the glomerular space and tubules, and degenerative changes in the tubular epithelium. (Magnification, ×280; reduced 3/10.)

There were striking changes in the coronary arteries of three animals. These consisted of marked edema and focal fibrinoid necrosis of the entire wall with a diffuse infiltration of inflammatory cells as seen in the larger arteries (Fig. 2, *C*). The inflammatory exudate frequently extended well outside the adventitia. No arteritis was observed outside the heart. (e) Kidneys. Significant changes were seen in the kidneys of six of the fourteen animals (Fig. 2, *D*). These consisted of marked swelling and increase in mononuclear cells of the

glomerular tufts. Adhesions between the tuft and the capsule were seen occasionally, and almost all the involved glomeruli were filled with protein precipitate. The proximal convoluted tubules of these nephrons were frequently dilated and filled with protein precipitate or erythrocytes. The lining cells were flattened but intact. Hyaline droplets were not conspicuous. (f) Spleen. Some degree of hyperplasia of the splenic lymphoid tissue was seen in almost all the animals in this experiment. In six of them, the reaction was considered severe and was accompanied by a marked hyperplasia of the large mononuclear phagocytes, as well as polymorphonuclear leukocytes. No instance of the severe granulomatous reaction described by Germuth[38] was seen, but in his series these were found at twelve days and had largely subsided at fifteen days.

EXPERIMENT II. ELECTROPHORETIC, TOTAL NITROGEN, ANTIBODY-N, AND PATHOLOGIC CHANGES IN SENSITIZED RABBITS TREATED WITH CORTISONE

On the first day of the experiment, three animals serving as controls were injected in the marginal ear vein with 2.5 ml. per kilogram body weight of sterile isotonic saline, and fifteen rabbits were similarly administered bovine plasma albumin in a dosage of 250 mg. per kilogram body weight. Immediately afterward, all rabbits were started on cortisone therapy, 10 mg. intramuscularly once daily for ten days and 5 mg. once daily for the next four days. All animals remained in good condition, with no significant weight loss, until the time of sacrifice on the fifteenth day. Serum samples were analyzed electrophoretically, for quantitative antibody content and for total protein.

Results.—

A. *Electrophoretic analyses:* Table III shows the protein components found in a representative number of sera prior to sensitization and also lists percentages of components in the sera of all animals after sensitization and cortisone therapy. The dotted line in Fig. 1 illustrates a typical pattern obtained at the conclusion of this experiment. It shows changes in the pattern of sensitized and cortisone-treated animals. Examination of these data revealed none of the sharp changes found in Experiment I. The only significant change in patterns after sensitization and cortisone therapy was found in an increase in the α_2 globulin; this was not of a high degree of significance. The decrease in γ globulin showed only a tendency toward significance. It is apparent that cortisone exerted quite a marked effect on the electrophoretic pattern of sensitized rabbits.

The sera of a representative number of this group of animals (including those showing high antibody content) were analyzed for total nitrogen, as stated previously, and these data were converted to total protein figures. Results are listed in Table III. As noted in the previous experiment, only the usual minor variations of rabbit blood proteins can be seen among these samples.

B. *Quantitative antibody-N in cortisone-treated sensitized rabbits:* Table III indicates an appreciable quantity of antibody in two rabbits and small amounts in four others. These determinations were made at the time of sacrifice (that is, fourteen days after sensitization), the cortisone having been ad-

TABLE III. ANALYSES OF SERA BEFORE AND AFTER SENSITIZATION AND CORTISONE THERAPY IN EXPERIMENT II.

RABBIT NUMBER	RELATIVE PERCENTAGES										A/G		TOTAL PROTEIN (GM. PER CENT)		ANTIBODY-N (MG.N/ML.)
	A		α_1		α_2		β		γ						
	b	a	b	a	b	a	b	a	b	a	b	a	b	a	a
304	46.0	53.8	3.3	4.0	11.6	11.4	15.4	16.9	23.7	13.9	0.85	1.16	6.3	7.0	0.008
305		47.2		6.1		24.3		12.7		9.7		0.89			0.002
306		38.6		2.4		22.8		19.1		17.1		0.63	5.1	4.7	0.046
307	60.6	64.9	4.4	4.5	11.6	9.6	13.9	12.0	9.5	9.0	1.54	1.84			0.0
308		53.2		5.4		19.9		12.9		8.6		1.14			0.001
309	61.3	71.3	5.5	3.1	6.7	6.3	11.7	12.0	14.7	7.3	1.59	2.49			0.0
310	67.0	78.0	4.1	3.0	9.3	5.3	11.3	9.9	8.3	3.8	2.03	3.56			0.0
311		65.1		9.7		12.6		8.2		4.4		1.87			0.0
312		59.2		5.8		16.3		13.3		5.4		1.45			0.0
313		51.6		5.1		18.5		14.6		10.2		1.06			0.001
314	52.4	48.4	3.3	4.0	11.9	24.5	13.3	13.2	19.1	9.9	1.10	0.94	5.6	6.4	0.0
315	67.3	71.2	3.9	4.8	8.5	11.2	13.7	5.6	6.5	7.2	2.06	2.47			0.0
316		53.8		4.3		10.5		24.3		7.1		1.16	5.1	8.0	0.037
317	56.3	57.4	3.6	5.8	10.0	10.5	12.4	15.8	17.7	10.5	1.28	1.35	6.2	6.3	0.0
318		58.7		12.1		14.9		8.6		5.7		1.42			0.0
Mean	58.7	58.2	4.0	5.3	9.9	14.6	13.1	13.3	14.2	8.7	1.49	1.56			
Standard error of mean	2.93	2.72	0.30	0.62	0.73	1.61	0.53	1.20	2.41	0.91	0.17	0.20			
Controls															
301	64.2	68.6	5.4	3.9	7.8	9.1	16.2	15.1	6.4	3.3	1.80	2.18	5.8	8.0	0.0
302															0.0
303	63.2	56.3	3.0	12.0	8.3	6.3	13.6	17.7	12.0	7.6	1.71	1.29			0.0

b = Before
a = After

ministered throughout the whole experiment as indicated previously. It is obvious that cortisone therapy, under the conditions of this experiment, had no appreciable effect on antibody production.

C. *Pathology:* The three control animals in this series showed no abnormality except for the presence of pneumonia in Rabbit 303. In the sensitized group, only one animal showed changes in the coronary arteries similar to those noted in the first experiment. This represents an incidence of 6.6 per cent, as compared with 22 per cent in the initial experiment. Two animals showed kidney changes resembling those seen in the initial experiment. This represented 13.3 per cent of the experimental group, as compared with 44 per cent in the initial experiment. The hyperplasia of the spleen was less marked and was present in five of eleven animals examined, or 46 per cent, as compared with 93 per cent in the untreated series. In none of the animals were subintimal, endocardial, or myocardial lesions noted (Table IV).

TABLE IV. SUMMARY OF ANATOMIC FINDINGS IN EXPERIMENT II. TISSUES EXAMINED IN SENSITIZED, CORTISONE-TREATED ANIMALS

ANIMAL NUMBER	SUBENDOTHELIAL INFILTRATION	ARTERITIS	VALVE LESIONS	FOCAL MYOCARDITIS	GLOMERULONEPHRITIS	SPLEEN HYPERPLASIA
301	0	0	0	0	0	–
302	0	0	0	0	0	–
303	0	0	0	0	0	–
304	0	0	0	0	2+	0
305	0	0	0	0	0	–
306	0	0	0	0	0	–
307	0	0	0	0	0	0
308	0	0	0	0	0	2+
309	0	0	0	0	0	–
310	0	0	0	0	0	–
311	0	0	0	0	0	0
312	0	0	0	0	0	0
313	0	0	0	0	0	0
314	0	0	0	0	3+	3+
315	0	0	0	0	0	2+
316	0	2+	0	0	0	2+
317	0	0	0	0	0	0
318	0	0	0	0	0	3+
	–	6.6%	–	–	13.3%	–

0 = Negative
– = Not examined

DISCUSSION

Dixon and co-workers[39, 40] have reported that the intravenous injection of antigen is followed by its elimination from the circulation in twelve to fourteen days, after which time circulating antibody may be detected. Germuth[38] has correlated these findings with observations of the pathologic lesions of hypersensitivity. He found that tissue changes occur during, and particularly at the end of, the antigen clearance phase, disappearing as antibody begins to appear.

In our own work, pathologic lesions were observed fourteen days after sensitization with bovine plasma albumin. Only two of the fourteen sensitized animals developed appreciable amounts of antibody in the serum. The pathologic changes in these two animals were comparable to those observed in others

in the series. It seems possible that these rabbits reacted to sensitization with such a large antibody response that antigen was eliminated earlier than in the other animals which were still in the "immune phase" of antigen elimination. These results, although differing only in a quantitative fashion from those of Germuth,[38] are not to be unexpected in biologic experiments such as this. It is interesting to note that Hawn and Janeway[41] observed acute lesions only when antigen was present and before antibody appeared in the circulation. According to Sternberger and associates,[42] when tissue lesions begin to appear antibody is absent because soluble antigen-antibody complexes form and are not detectable by ordinary serologic procedures. After all free antigen has been cleared from the circulation, free antibody can be demonstrated.

When cortisone is given throughout the sensitization period that follows administration of bovine plasma albumin, the appearance of pathologic lesions is suppressed.[43-48] This may be brought about through the known suppressive influence of cortisone on inflammation in general. There is still another explanation. It is known that these agents suppress protein synthesis[49] and cause lympholysis. It has been suggested that, through these effects, there may be interference with the immune mechanism responsible for such lesions.

We have found that sera obtained from rabbits prior to sensitization produced normal electrophoretic patterns. Sera obtained fourteen days after sensitization with bovine plasma albumin gave patterns characterized by an increase in γ globulin and decreases in albumin and α_1 globulin, changes which we find can be prevented by the administration of cortisone. These results bear a strong similarity to those obtained by Reiner[52] on human beings suffering from lupus erythematosus. Initially, such patterns showed a lowered albumin content and a considerable elevation in α_2 and γ globulins. After a period of cortisone therapy, which produced a remission of clinical symptoms, the albumin and γ globulin components progressed toward normal levels, while the α_2 fraction remained unchanged. It would seem, from this information, that cortisone may offset in some manner the cause of the albumin and γ globulin changes, while giving rise to a new effect which is manifest in an α_2 globulin increase in previously sensitized animals as noted in our experiment. It is interesting to point out that Cooke and his co-workers[53] have found electrophoretic changes in the sera of patients with intrinsic asthma, but not in those with extrinsic asthma. These patterns resembled those found in other infections and in lupus erythematosus disseminatus, and were reverted to normal by ACTH. In the limited studies available, electrophoretic pattern changes were also observed in periarteritis nodosa. These showed a slight elevation in γ globulin, a decrease in albumin, and, in some instances, an increase in α_2 globulin.[37]

One might argue that the increased γ globulin levels found in sensitized animals should indicate increased antibody production and should be reflected in the antibody-nitrogen analyses. Several important points regarding antibody production must be kept in mind, however. The type and amount of such production are dependent upon the antigen used, the species immunized, the route of immunization, and the duration of immunization. The classical experiments of

Tiselius and Kabat,[32] in which a direct correlation between increased γ globulin and antibody production was shown, were performed on hyperimmune sera obtained from animals subjected to a series of antigen injections in order to produce maximum antibody. In the present work, only one injection of antigen was made; there was no attempt to produce maximum antibody in a hyperimmune serum by the usual immunization series of injections. Even in hyperimmune sera, the increase in globulin does not always correspond to the antibody formed but, rather, a considerable nonspecific stimulation for the formation of globulin also takes place.[54] Boyd and Bernard[55] have found that rabbits injected with antigen three times a week for several months showed great increases in globulins, but that these increases were not all, or even chiefly, attributable to the specific antibodies produced. As a rule, they noted that the antibody produced was much less than the increase in globulin. The identification of all γ globulins with antibodies and vice versa is an oversimplification. This has been pointed out very clearly by Gutman.[56] Bjorneboe[57] has found that rabbit antisera to pneumococcal vaccine may develop appreciable globulin increases which are not in the form of specific antibody. It may be further pointed out that in many infections clinically important antibodies are formed in amounts too small to cause any measurable change in electrophoretic patterns, even though they are easily detectable by serologic methods.[56, 58] One may thus conclude that increased γ globulin is not necessarily and always indicative of antibody production but, rather, may be the result of some other mechanism involved in protein synthesis.

Our observation that sensitization with bovine plasma albumin as antigen causes a decrease in serum albumin and in α_1 globulin cannot be fully interpreted because of a lack of more fundamental information along the lines of protein equilibria. It may be stated, however, that albumin decreases of this type are quite common in febrile illness and are not particularly specific, having been noted in a variety of pathologic conditions.[56, 59] Since the present extent of our knowledge concerning protein function and synthesis is still quite limited, we prefer, rather than to speculate further into the significance of the observed changes in blood proteins, to merely report our findings as such and reserve judgment on their importance for a more appropriate time in the future.

SUMMARY

1. Rabbits were sensitized with bovine plasma albumin and sacrificed fourteen days later, at which time tissues were examined histopathologically. Blood samples were taken before and after sensitization; the sera were examined electrophoretically and for total nitrogen and the presence of antibody.

2. Lesions of the type seen in experimental hypersensitiveness were found in a high percentage of the sensitized animals. Electrophoretically, these animals showed decreased albumin and α_1 globulin accompanied by increased γ globulin levels. Only two animals showed measurable antibody production. The total nitrogen was unchanged.

3. Another group of rabbits, similarly sensitized, was treated with cortisone. The occurrence of lesions was sharply diminished and all electrophoretic changes were prevented. No effect on antibodies was noted by this technique.

4. The possible interrelationship of these findings is discussed.

REFERENCES

1. Klinge, F.: Die Eiweissüberempflindlichkeit (Gewebsanaphylaxie) der Gelenke. Experimentelle pathologische—anatomische studie zur Pathogenese des Gelenkrheumatismus, Beitr. path. u. allg. Path. **83**: 185, 1929.
2. Klinge, F.: Der Rheumatisms. Pathologische-Anatomische und experimentelle pathologische Tatsachen und ihre Auswertung für das artzliche Rheumaproblem, Ergebn. allg. Path. u. Path. Anat. **27**: 1-336, 1933.
3. Klemperer, P., Pollack, A. S., and Baehr, G.: Diffuse Collagen Disease, J. A. M. A. **119**: 331, 1942.
4. Klemperer, P.: Diseases of the Collagen System, Bull. New York Acad. Med. **23**: 581-587, 1947.
5. Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions, Ann. Int. Med. **28**: 1-14, 1948.
6. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**: 123, 1942.
7. Marine, D., and Bauman, E. J.: Periarteritis Nodosa-Like Lesions in Rats Fed Thiouracil, Arch. Path. **39**: 325, 1945.
8. Rich, A. R.: Periarteritis Nodosa Hypersensitivity to Iodine as One of the Causes, Rev. Asoc. méd. argent. **60**: 816, 1946.
9. Reimann, H. A., Price, A. H., and Herbert, P. A.: Trichinosis and Periarteritis, Differential Diagnosis and Possible Relationship, J. A. M. A. **122**: 274, 1943.
10. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**: 65, 1943.
11. Rich, A. R., and Gregory, J. E.: Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **75**: 115, 1944.
12. Rich, A. R., and Gregory, J. E.: Experimental Evidence That Lesions With the Basic Characteristics of Rheumatic Carditis Can Result From Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**: 239-264, 1943.
13. Alston, J. M., Cheng, K. K., and Short, R. H. D.: Unsuccessful Attempts to Produce Periarteritis Nodosa Experimentally, J. Path. & Bact. **59**: 490, 1947.
14. More, R. H., and McLean, C. R.: Lesions of Hypersensitivity Induced in Rabbits by Massive Injections of Horse Serum, Am. J. Path. **25**: 581-587, 1949.
15. Ehrich, W. E., Seifter, J., and Forman, C.: Experimental Serum Disease; A Pathogenic Study, J. Exper. Med. **89**: 23-35, 1949.
16. Miller, C. P.: Spontaneous Interstitial Myocarditis in Rabbits, J. Exper. Med. **40**: 543-551, 1924.
17. Ehrich, W. E.: The Significance of Tissue Reactions Caused by Antigens, J. A. M. A. **135**: 94-97, 1947.
18. Miale, J. B.: The Manifestations and Mechanisms of Vascular Allergy; A Critical Review, Ann. Allergy **7**: 124-149, 1949.
19. Peale, A. R., Gildersleeve, M., and Luchesi, P. F.: Periarteritis Nodosa Complicating Scarlet Fever, Am. J. Dis. Child. **72**: 1310, 1946.
20. Rhoads, P. S., and Afremow, M. L.: The Significance of Joint Pains Caused by Sterile Streptococcus Toxin, Ann. Int. Med. **19**: 60, 1943.
21. Healey, C. E.: The Causes of Joint Pain Occurring During Active Immunization With Scarlet Fever Streptococcus Toxin, J. A. M. A. **108**: 628, 1937.
22. Ayvazian, L. F., and Badger, T. L.: Disseminated Lupus Erythematosus in Student Nurses, New England J. Med. **239**: 565, 1948.
23. Ferraro, A.: Allergic Brain Changes in Post-Scarlatinal Encephalitis, J. Neuropath. & Exper. Neurol. **3**: 239, 1944.
24. Watson, R. F., Rothbard, S., and Swift, H. F.: Relationship of Post-Scarlatinal Arthritis and Carditis to Rheumatic Fever, J. A. M. A. **128**: 1145, 1945.
25. Criep, L. H., and Mayer, L. D.: Experimental Collagen Disease From Hypersensitization to Streptococcus Toxin, J. ALLERGY **20**: 243-254, 1949.
26. Criep, L. H., Mayer, L. D., and Cohen, S. G.: The Effect of X-radiation on Hypersensitiveness, J. ALLERGY **21**: 373-385, 1950.

27. Bukantz, S. C., Dammin, G. J., Wilson, K. S., Johnson, M. C., and Alexander, H. L.: Inhibitory Effect of Nitrogen Mustard (Bis Beta-Chlorethyl Amine) on Lesions of Experimental Serum Hypersensitiveness, Proc. Soc. Exper. Biol. & Med. **72**: 21-26, 1949.
28. Schwab, L., Moll, F. C., Hall, T., Brean, H., Kirk, M., Hawn, C. van Z., and Janeway, C. A.: Experimental Hypersensitivity in the Rabbit, Effect of Inhibition of Antibody Formation by X-radiation and Nitrogen Mustards on the Histologic and Serologic Sequences, and on the Behavior of Serum Complement Following Single Large Injections of Foreign Proteins, J. Exper. Med. **91**: 505-526, 1950.
29. Cohen, S. G., Mayer, L. D., and Criep, L. H.: The Experimental Production of Arteritis by Passive Sensitization, J. Immunol. **66**: 487-496, 1951.
30. Criep, L. H., Mayer, L. D., and Menchaca, O. E. L.: The Effect of Adrenalectomy on Experimental Hypersensitiveness, J. ALLERGY **22**: 314-329, 1951.
31. Kabat, E. A., and Mayer, M. M.: Experimental Immunochemistry, Springfield, Ill., 1948, Charles C Thomas.
32. Tiselius, A., and Kabat, E. A.: An Electrophoretic Study of Immune Sera and Purified Antibody Preparations, J. Exper. Med. **69**: 119, 1939.
33. Stull, A., Sherman, W. B., and Cooke, R. A.: The Association With Pseudoglobulin of the Skin Sensitizing Substance of Allergic (Hay Fever) Serum, J. ALLERGY **9**: 7, 1937.
34. Newell, J. M., Sterling, A., Oxman, M. F., Burden, S. S., and Krejci, L. E.: Electrophoretic Separation of the Antibody From Human Allergic Serum, J. ALLERGY **10**: 513, 1939.
35. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**: 196, 1943.
36. Vaughan, J. H., Bayles, T. B., and Favour, C. B.: The Response of Serum Gamma Globulin Level and Complement Titer to ACTH Therapy in Lupus Erythematosus Disseminatus, J. Lab. & Clin. Med. **37**: 698, 1951.
37. Wisenbaugh, P. E.: Effects of Cortisone and ACTH on Plasma Protein Electrophoretic Patterns, Lab. Invest. **1**: 332, 1952.
38. Germuth, F. G., Jr.: A Comparative Histologic and Immunologic Study in Rabbits of Induced Hypersensitivity of the Serum Sickness Type, J. Exper. Med. **97**: 257, 1953.
39. Dixon, F. J., Bukantz, S. C., and Dammin, G. J.: The Effect of Sensitization and X-radiation on the Metabolism of I^{131} Labeled Proteins, Science **113**: 274, 1951.
40. Dixon, F. J., Bukantz, S. C., Dammin, G. J., and Talmadge, D. W.: Fate of I^{131} Labeled Bovine Gamma Globulin in Rabbits, Federation Proc. **10**: 553, 1951.
41. Hawn, C. van Z., and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, J. Exper. Med. **85**: 571, 1947.
42. Sternberger, L. A., Maltaner, F., and DeWeerdt, J.: The Estimation of Circulating Antibody-Antigen Complex, J. Exper. Med. **98**: 451, 1953.
43. Germuth, F. G., Jr.: The Mechanism of Action of Cortisone in Experimental Hypersensitivity. II. Hypersensitivity of the Serum Sickness Type, J. Exper. Med. **98**: 1, 1953.
44. Berthrong, M., Dich, A. R., and Griffith, P. C.: Study of Effect of Adrenocorticotropic Hormone (ACTH) Upon Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **86**: 131, 1950.
45. Rich, A. R., Berthrong, M., and Bennett, I. L., Jr.: Effect of Cortisone Upon Experimental Cardiovascular and Renal Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **87**: 549, 1950.
46. Bennett, I. L., Jr., Berthrong, M., and Rich, A. R.: Further Study of the Effect of Adrenocorticotropic Hormone Upon the Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **88**: 197, 1951.
47. Seifter, J., Ehrich, W. E., Begany, A. J., and Warren, G. H.: Effects of Cortisone, Hyaluronidase, Desoxycorticosterone, and Artisone on Experimental Serum Disease in Rabbits, Proc. Exper. Biol. & Med. **75**: 337, 1950.
48. Germuth, F. G., Jr., and Ottinger, B.: Effect of 17-Hydroxy-11-Dehydrocorticosterone and of ACTH on Arthus Reaction and Antibody Formation in the Rabbit, Proc. Soc. Exper. Biol. & Med. **74**: 815, 1950.
49. Clark, I.: Effect of Cortisone on Protein Metabolism in the Rat as Studied With Isotopic Glycine, Federation Proc. **9**: 161, 1950.
50. Fischel, E.: Discussion, ACTH and Antibodies, Proc. 2nd Clin. ACTH Conference, Vol. 1, New York, 1951, The Blakiston Company, p. 492.
51. Germuth, F. G., Jr., Oyama, J., and Ottinger, B.: Mechanism of Action of 17-Hydroxy-11-Dehydrocorticosterone and of Adrenocorticotropic Hormone in Experimental Hypersensitivity in Rabbits, J. Exper. Med. **94**: 139, 1951.
52. Reiner, M.: Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus, Proc. Soc. Exper. Biol. & Med. **74**: 529, 1950.
53. Cooke, R. A., Sherman, W. B., Menzel, A. E. O., Chapin, H. B., Howell, C. M., Scott, R. B., Myers, P. A., and Downing, L. M.: ACTH and Cortisone in Allergic Diseases, J. ALLERGY **22**: 211-236, 1951.

54. Kabat, E. A.: Immunochemistry of the Proteins, J. Immunol. 47: 513, 1943.
55. Boyd, W. C., and Bernard, H.: Quantitative Changes in Antibodies and Globulin Fractions in Sera of Rabbits Injected With Several Antigens, J. Immunol. 33: 111, 1937.
56. Gutman, A. B.: The Plasma Proteins in Disease, Advances Protein Chem. 4: 155, 1948.
57. Bjorneboe, M.: Serum Proteins During Immunization, Acta. path. et microbiol. scandinav. 20: 221, 1943.
58. Koprowski, H., Richmond, G., and Moore, D. H.: Electrophoretic Study of Antiviral Sera, J. Exper. Med. 85: 515, 1947.
59. Luetscher, J. A., Jr.: Biological and Medical Applications of Electrophoresis, Physiol. Rev. 27: 621, 1947.

AEROALLERGEN STUDIES WITH THE MOLECULAR FILTER MEMBRANE

CLIFFORD W. GURNEY, M.D., AND SYDENHAM CRYST, M.D.,* ANN ARBOR, MICH.

INTRODUCTION

AEROALLERGEN studies were performed in Ann Arbor, Michigan, during the summer of 1954. The specific goal was to examine the patterns of fluctuation of ragweed pollen concentration through twenty-four-hour cycles. Since this information was being obtained, it was thought to be of some interest to see to what degree fluctuations of patients' symptoms might be related to change in ragweed pollen concentration.

A massive volume of literature pertaining to atmospheric sampling of ragweed pollen has been recorded in the last twenty-five years, culminating recently in a detailed account of regional distribution of aeroallergens.[1] Most of the data accumulated have been concerned with samples obtained in consecutive twenty-four-hour periods; there have been occasional investigations of diurnal ragweed pollen variation. In 1929, Durham[2] stated, "An hourly study, made during the height of the season, shows that most of the day's yield of pollen was thrown into the air early in the morning at the usual time of ripening of the male flowers. By midnight, the bulk of this load had been precipitated." This conclusion is based on data obtained over a single twenty-four-hour period. Excellent studies pertaining to the diurnal variation in incidence of grass pollen have been performed in Great Britain by Hyde and Williams[3] employing a modification of the gravity sampling technique. Since dissemination of ragweed pollen is not a problem in Great Britain, these investigators did not include results pertaining to this aeroallergen. More recently, Smith and Rooks,[4] employing an impingement type of volumetric sampler, concluded: "Only 10 per cent of the pollen collected for the twenty-four-hour periods was collected from 6:00 P.M to 6:00 A.M. during the months of August and September." This is consistent with the results of Jones,[5] who used a gravity type sampler. However, Wilmer and Cobe,[6] employing a modification of the gravity sampler, obtained counts every two hours at nine different levels, and it is interesting to note the high values obtained at 5:30 A.M.

It has long been recognized that the ideal method of obtaining estimates of aeroallergens would be the actual filtration of a known volume of air. Precise quantitative pollen counts could then be made, and they would have volumetric significance. Previous methods of aeroallergen study have been ingenious compromises with this ideal technique and the reality that no filter was available to perform this service. The variety of techniques employed

Received for publication March 7, 1955.

*From the Department of Internal Medicine, University of Michigan Medical School.

(hair dryers,[7] air centrifuges,[8] a vacuum cleaner,[9] shielded slides and slides exposed to the wind,[10] cascade impactors, etc.) testify only to the generally unsatisfactory nature of available techniques. Nor did erudite discussions of Stokes's law and Scheppegrell's modification[11] serve to place gravity sampling on any firmer foundation. Perhaps the objections to the gravity sampling technique have been expressed most succinctly by Hewson[12] when he stated: "The number of particles which are impacted per unit time on the slide must be a complex function of their size and of the contemporary atmospheric turbulence; the impaction rate will vary with the fluctuating wind speed and

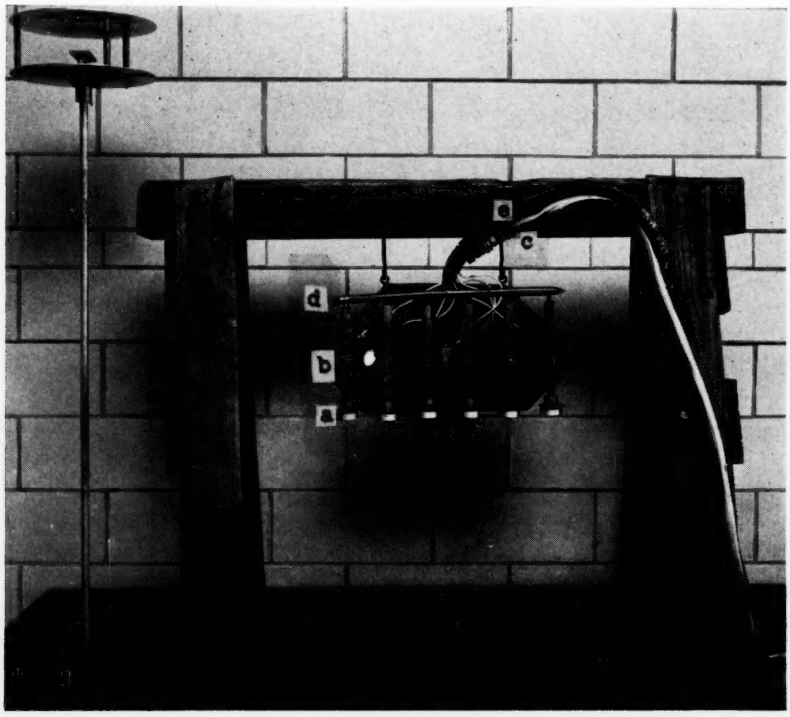


Fig. 1.—The portion of the apparatus containing the molecular membrane filters, and a conventional gravity sampler.

This portion of the apparatus was photographed in the laboratory. During the course of the experiment, it was located on an unobstructed roof six floors above the ground.

A molecular filter membrane is present in each of the metal heads (*a*). Electrical valves (*b*) are connected to control apparatus by way of wires coming through conduit (*c*). When each valve in its turn is open, air passes through the filter into the metal tube (*d*) and into the tube (*e*) which is attached to a vacuum pump.

angle of attack on the coated slide. A more accurate conversion factor which is a function of gustiness might be specified, but the gustiness itself would then have to be measured, which introduces a complication. A direct, simple, and accurate measuring technique is greatly to be preferred," and by Fletcher and Veltz,[13] who stated that "probably because of high degree of turbulance associated with variation in air movement, pollen grains actually land on an exposed slide more in accordance with the laws of chance than with laws of

gravity." Throughout all these early studies, the allergist readily called upon his colleagues in physics, botany, and engineering for help in solving the problem. The technique which we adapted does likewise.

The method to be described herein is complex and the apparatus is costly. It is not intended to replace the conventional method of pollen counting at the present time, but we believe that it has value as a research tool.

THE METHOD

In recent years a synthetic filter, known as the molecular filter membrane,[14] became available. The filter, 1 inch in diameter, is paper-thin and contains 5 by 10^7 pores per square centimeter. Particles as small as 0.2 micron are quantitatively removed from an air stream passing through the filter. A simple compact pump is available for obtaining single samples of any desired volume of air but, since we wished to obtain frequent determinations

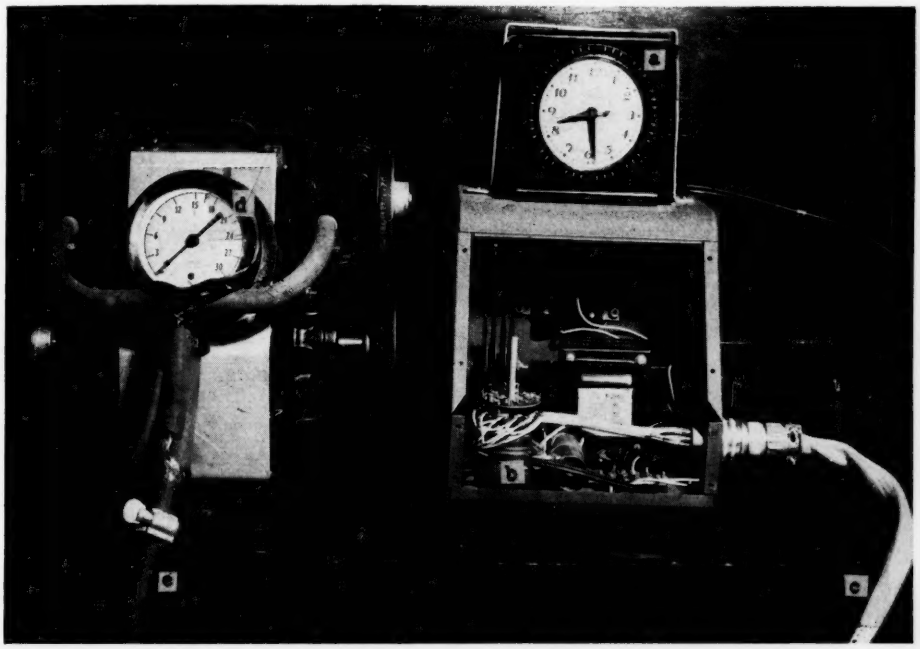


Fig. 2.—Apparatus which controls periodic sampling.
Telechron clock (*a*) activates solenoid (*b*), permitting current to flow to a different valve every four hours through conduit (*c*). Vacuum pump (*d*) is in operation while each valve is open, and is connected with the heads containing the molecular filter by the tubing (*e*).

during each twenty-four-hour period, a more complex apparatus was necessary. Ours consisted of a battery of six such filters connected to an air pump and controlled by electrically operated valves (Figs. 1 and 2). A timing device was added so that serial samples could be obtained throughout the day. We obtained thirty-minute samples every four hours, giving six samples in each twenty-four-hour period. The filters were removed and mounted on slides, and total ragweed counts were made each day. Each used filter, con-

taining all aeroallergens of particle sizes greater than 0.2 micron obtained from a volume of 270 liters of air, was counted in its entirety. Pollen and fungi could be identified as readily on these filters as on conventional gravity slides. A separate report describes in detail the specifications and operation of our apparatus.[15]

Preliminary studies indicated that if the battery of filters pointed into the wind there was a significant increase of pollen when compared with simultaneous determinations taken down wind. In order to nullify the effect of wind, the filters were directed downward when further studies indicated that there was no significant loss of pollen. The apparatus was placed on an unobstructed roof six floors above the ground.

DATE: SUN., MON., TUES., WED., THURS., FRI., SAT., AUG. SEPT._____

	2:00 AM-6:00 AM	6:00 AM-10:00 AM	10:00 AM-2:00 PM	2:00 PM-6:00 PM	6:00 PM-10:00 PM	10:00 PM-2:00 AM
STUFFINESS.						
WATERING OF NOSE.						
SNEEZING.						
ITCHING: NOSE OR EYES.						
WHEEZING						
ANTIHISTAMINES.						
OTHER MEDICATIONS.						

REMARKS:

0 = NO SYMPTOMS
+ = MILD TO MODERATE
++ = SEVERE SYMPTOMS
V = OUT OF TOWN
S = SLEEPING

CODE #_____

Fig. 3.—A sample postcard. Each patient was supplied with one such postcard for each day of the 1954 ragweed season.

Seventeen patients with ragweed sensitivity, living in or near Ann Arbor, were supplied with postcards (Fig. 3) on which they recorded severity of symptoms according to a code at the bottom right-hand corner. An arbitrary index of symptom severity was calculated by adding the numbers of plusses in each time period for all the patients and dividing this sum by the number of patients reporting for each period. On those days when any patient was away from the Ann Arbor vicinity, his reports were excluded from calculation of that day's index of symptoms. Thus, if all seventeen patients experienced the maximum symptoms from 6:00 A.M. to 10:00 A.M. on a given day (recording ++ for each of the five symptoms—stuffiness, rhinorrhea, sneezing, itching of nose, and wheezing) totaling ten +'s per patient, the total would be 170 for the four-hour period. If this figure is divided by seventeen (the number of patients reporting), the index of symptoms would be 10. The index is thus corrected for absence of patients, failure to reply, incorrect dating of postcard, or masking of allergic symptoms by other illness.

RESULTS

The fluctuation of pollen concentration is shown in Figs. 4 and 5; each block represents one day, and the date is shown on the abscissa. The initial value each day is the 8:00 A.M. determination, and the following values rep-

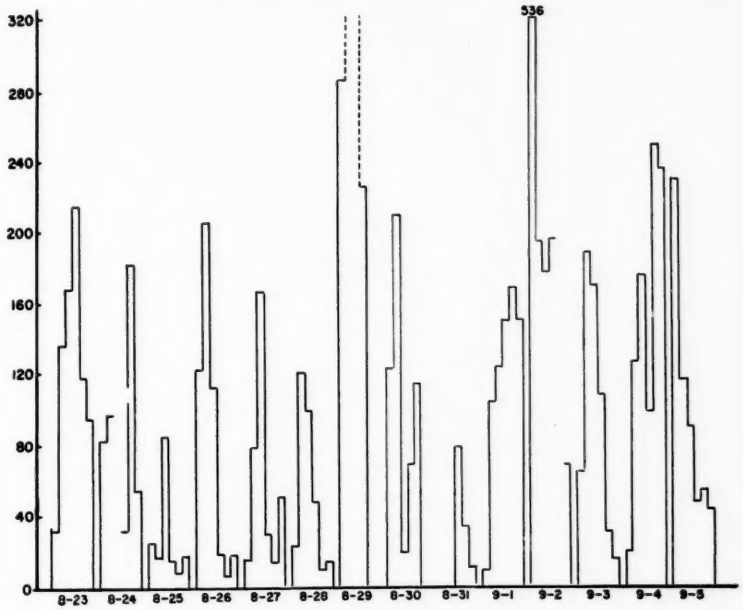


Fig. 4.—Fluctuation of ragweed pollen concentration. Dates are recorded along abscissa. Values along ordinate represent ragweed pollen grains per 270 liters.

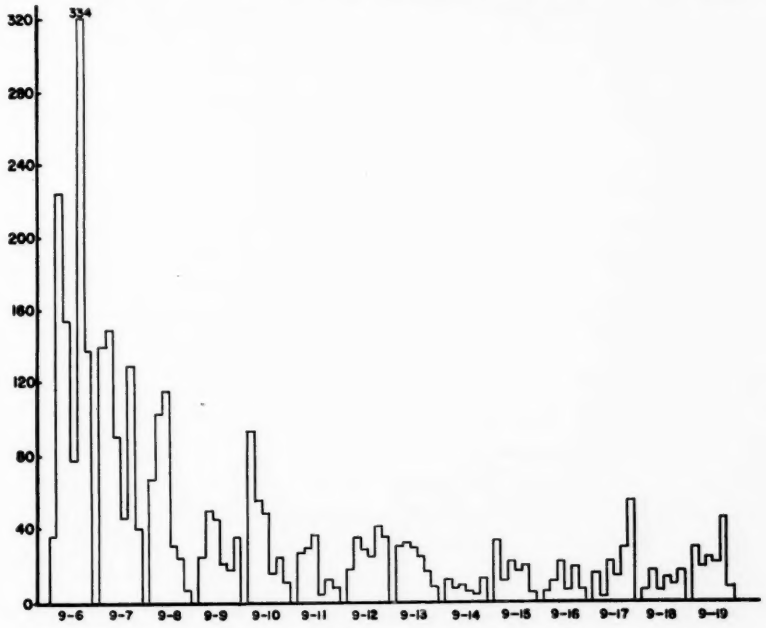


Fig. 5.—For explanation, see Fig. 4.

resent the determinations every four hours thereafter; the last value in each day's bar represents the 4:00 A.M. value for the following day. The method of graphing was chosen, as it seemed likely that the ragweed pollen in the atmosphere at midnight and 4:00 A.M. largely represented carry-over from the pollen liberated in the previous twenty-four-hour period. The height of each individual bar represents the number of ragweed pollen grains on the corresponding filter. The pollen was obtained from the 270 liters of air which passed through the filter during the half-hour that its specific valve was open.

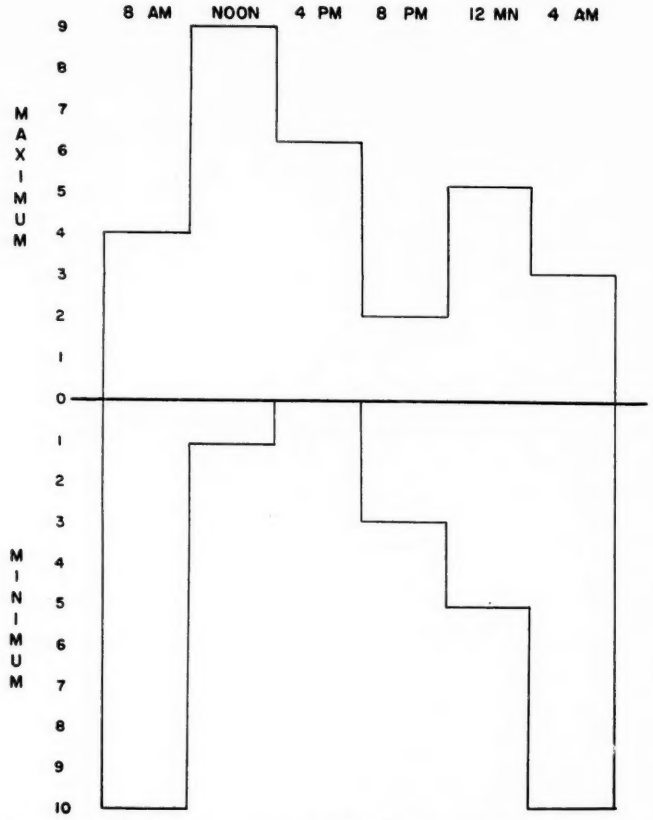


Fig. 6.—Frequency of the daily maximum and minimum pollen concentrations at each of the sampling periods.

The ordinate, then, shows the amount of pollen contained in approximately 10 cubic feet of air (270 liters = 9.5 cubic feet) during each of the time periods shown on the abscissa. On two occasions the results were too high to be charted using the coordinate values employed; these results are indicated in the appropriate space.

Several conclusions are apparent from Figs. 4 and 5. First, the usual pattern of fluctuation of ragweed pollen concentration is for higher values during the midday and lower values in early morning and late at night, as would be anticipated. Second, although pollen is liberated in the late morning,[5]

these studies show that high concentrations of ragweed pollen were present at midnight and 4:00 A.M. on several occasions. For example, on August 30, September 4, and September 6, late peaks occurred, on the latter two occasions with the daily maximum concentrations occurring at midnight.

Fig. 6 represents the incidence of maximum and minimum concentrations in each four-hour period. Of the twenty-nine complete daily cycles shown, twenty-three were taken from Figs. 4 and 5 (in each of the instances where complete data were available for the twenty-four-hour period). The data for the other six days were obtained prior to Aug. 23, 1954, at a time when the orientation of the filters was upward rather than downward, and we have not included them in Fig. 4, as they are not comparable. The difference, however, does not affect the time of maximum pollen concentrations. On the basis of the information in Fig. 6, one can again appreciate the fact that, although a pattern appears to emerge with higher concentrations occurring at noon and 4:00 P.M. and lower concentrations occurring from midnight through 8:00 A.M., the maximum and minimum concentrations can occur at any time with the exception of 4:00 P.M., when no minima are recorded. We should like to emphasize that these generalizations stem from a limited amount of data; many future determinations are necessary if they are to be verified. The patterns described apply to a sixth-floor level and, since simultaneous ground-level determinations were not obtained, we do not know whether the same fluctuations occur at zero elevation.

Figs. 7 and 8 record the fluctuations of patients' symptoms. Each fragment of the broken line represents one day, extending consecutively from Aug. 23, 1954. Only 6:00 A.M. to 10:00 P.M. periods are recorded; the 10:00 P.M. to 2:00 A.M. and 2:00 A.M. to 6:00 A.M. indices were omitted because it was found that most patients were sleeping during these periods and, therefore, did not record symptoms. Calculating the index of symptoms at times when the patients with severe allergies were awake because of allergic difficulty, excluding those patients whose disease was of less severity but whose symptoms entered into the calculations during the day, would give falsely high values for indices during the night.

The preceding data suggest that fluctuations of symptoms of patients in and around Ann Arbor fail to show any close correlation with ragweed concentration as determined at the sixth floor. Possibly the concentrations of ragweed at the sixth floor may be different from those on the ground, and the variations of ragweed concentration in different locations probably are quite marked. Further, the concentration of dust, fungus, and other aeroallergens, to which some of the patients were also sensitive, would not necessarily parallel ragweed. Perhaps of greater importance is the pattern of fluctuation. It will be seen that, with one exception (September 18), symptoms were always higher in the morning, falling to a lower value at noon. Frequently there was a secondary rise in symptoms in the evening; this value sometimes exceeded the 8:00 A.M. determination. With one exception, there is a consistent pattern of more difficulty in the morning and improvement at

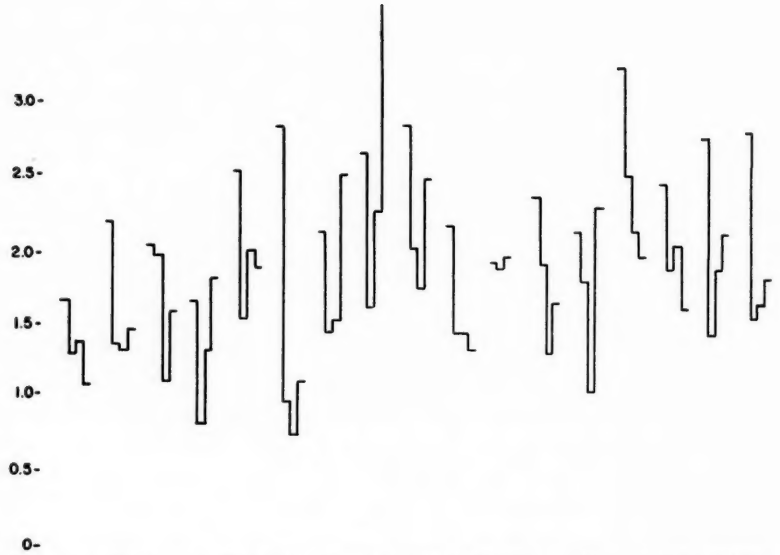


Fig. 7.—Index of symptoms. Each day is represented by one portion of the broken line, beginning on Aug. 23, 1954 (left), and extending through Sept. 8, 1954 (right).

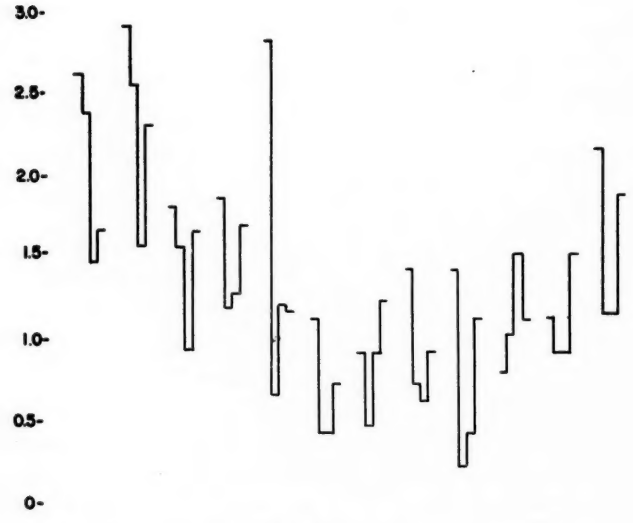


Fig. 8.—For explanation, see Fig. 7. Sept. 9, 1954, through Sept. 20, 1954.

noon, frequently in spite of a marked rise of ragweed concentration during this interval. This pattern of symptoms would seem to be worthy of further investigation.

CONCLUSIONS

1. A new method of aeroallergen determinations is discussed.

2. Fluctuations in ragweed pollen concentration throughout twenty-four-hour cycles are recorded. A pattern of higher ragweed concentrations at midday and lower concentrations in the late evening and early morning hours is suggested, although there are exceptions to this tendency.

3. The symptoms of the patients studied do not correlate readily with ragweed concentration, but suggest an interesting independent pattern. Manifestations of allergic disease were more prominent in the morning and decreased at midday, often despite a marked increase in ragweed levels.

4. In view of the lack of correlation between fluctuations of aeroallergen concentrations and severity of patients' symptoms, there does not appear to be sufficient reason at this time to recommend the replacement of the simple method of aeroallergen sampling presently used by a precise, though more complicated, volumetric method of sampling.

We wish to acknowledge our indebtedness to Dr. John M. Sheldon of the Allergy Section, University of Michigan Hospital, and to Professor Wendell Hewson and Mr. William Hanson of the Engineering Research Institute of the University of Michigan for their advice, encouragement, and assistance.

REFERENCES

1. Samter, M., and Durham, O. C.: Regional Allergy of the United States, Canada, Mexico and Cuba, American Lecture Series No. 224, Springfield, Ill., 1955, Charles C Thomas.
2. Durham, O. C.: Co-operative Studies in Ragweed Pollen Incidence, J. ALLERGY **1**: 12, 1929-30.
3. Hyde, H. A., and Williams, D. A.: Studies in Atmospheric Pollen. II. Diurnal Variation in Incidence of Gross Pollen, New Phytologist **44**: 83, 1945.
4. Smith, R. D., and Rooks, R.: The Diurnal Variation of Air-Borne Ragweed Pollen as Determined by a Continuous Recording Particle Sampler and Implications of the Study, J. ALLERGY **25**: 36, 1954.
5. Jones, M. D.: Time of Day of Pollen Shedding of Some Hay Fever Plants, J. ALLERGY **23**: 247, 1952.
6. Wilmer, H. B., and Cobe, H. M.: Quantitative Survey of Pollen, J. ALLERGY **3**: 63, 1932.
7. Duke, W. W.: A Rapid and More Accurate Method of Determining the Pollen Concentration of the Air, J. A. M. A. **99**: 1686, 1932.
8. Durham, O. C.: Methods in Aerobiology, J. Aviation Med. **12**: 153, 1941.
9. Cocke, E. C.: A Method for Determining Pollen Concentration of the Air, J. ALLERGY **9**: 458, 1937-38.
10. Penfound, W. T., and Efron, B. G.: A Standardized Method for Pollen Air Analysis, Proc. Soc. Exper. Biol. & Med. **27**: 650, 1930.
11. Vaughan, W. T., and Black, J. H.: Practice of Allergy, St. Louis, 1954, The C. V. Mosby Company, pp. 447-451.
12. Hewson, E. W.: Some Aspects of the Dispersion of Pollens and Industrial Contaminants in Relation to Micrometeorology, University of Michigan Engineering Research Institute, Project 2160, Scientific Report Number 1, October, 1953.
13. Fletcher, A., and Veltz, C. J.: Pollens-Sampling and Control, Indust. Med. **19**: 129, 1950.
14. Goetz, A.: The Application of Molecular Filter Membranes to the Analysis of Aerosols, Am. J. Pub. Health **43**: 150, 1953.
15. Cryst, S., Gurney, C., and Hansen, W.: A Method for Determining Aero-Allergen Concentrations With the Molecular Filter Membrane, J. Lab. & Clin. Med. **46**: 471, 1955.

SENSITIZATION OF THE HUMAN SKIN

A Study of Location of Sites and of Exposure Time of Excitant

Max Grolnick, M.D., Brooklyn, N. Y.

IN PREVIOUS experiments of mine[1-3] in active sensitization of the skin of human beings with krameria, a plant extract, certain deductions made from the findings therein seemed applicable to the study of a method for testing the sensitizing potentials of chemicals (therapeutic, cosmetic, industrial, etc.) to which the skin may be exposed. Experimental studies in skin sensitization are readily carried out in animals, and are helpful in determining the general immunologic responses of the skin. They do not, however, accurately reflect what is occurring in the sensitized human skin. Man is generally considered to be the ideal test subject, the findings obtained representing a better guide to the prognostication of what eventually can be expected to happen to the human skin when it is exposed to a substance which is a potential sensitizer.

Sulzberger and Simon,[4] in studying why various arsphenamines differed in their properties to cause sensitization in treated subjects, planned experiments in active sensitization of guinea pigs with the drugs, aimed at determining the "sensitization index" of various lots of the drug. They stated, too, that information obtained concerning sensitization in another species was not necessarily directly applicable to arsphenamine sensitization in man. The term "sensitivity index" was employed by Rostenberg and Sulzberger[5] in a clinical evaluation of the results of patch tests on nearly 1,000 patients to indicate the measure of positive reactions to be expected in various dermatoses under consideration. Rostenberg and Kanof[6] compared the sensitizing capacities of two simple chemicals by actively sensitizing their subjects to both substances and comparing the incidence of sensitization to each. Various other techniques of sensitization with various substances are discussed by me[3] in a paragraph on factors in sensitization in eczematous contact type dermatitis.

In this presentation, the roles of exposure time and of location of exposure sites of the excitant will be analyzed, based on findings elicited in experimental studies of the factors concerned in the production of epidermal sensitization. These factors of time and of site location will then be varied in a number of technical procedures designed to determine the sensitizing potential of a known chemical substance in man.

The use of the prophetic patch test of Schwartz[7-9] is not now generally accepted. It is not felt that an initial patch test application for two to five days, followed fourteen to twenty-one days later by a one- to two-day challeng-

From the Divisions of Allergy, The Jewish Hospital of Brooklyn and the Maimonides Hospital.

Received for publication March 9, 1955.

ing test, is an adequate exposure for substances generally, unless the substance is a potent sensitizing material and/or a high concentration of it is used. In support of the latter exception can be offered the following several experiences, among others. Straus[10] sensitized the rhesus monkey by means of a single forty-eight-hour patch test with undiluted poison ivy oil; Wedroff and Dolgoff[11] rendered sensitive 70 per cent of their subjects (humans) by applying to the skin a single drop of a 10 per cent solution of dinitrochlorobenzene; Grolnick[1, 2] was able to sensitize the human skin by applying to the skin several drops of the fluid extract of krameria as a patch test for a one-, two-, or three-day period.

The present method of prophetic testing for meeting the requirements of the United States Food and Drug Administration is that which is recommended by Draize[12, 13] of the Department of Pharmacology. In this procedure, ten successive twenty-four-hour patch test applications are made every other day to varied parts of the body. A challenging test is applied two weeks after the last test. Draize believes that a "number of fresh exposures or insults" are "preferable to one continuous exposure." He predicates his recommendations on the belief that substances applied to the skin are quickly eliminated therefrom. No confirmatory evidence is offered for this view. This procedure of testing obviously is a great inconvenience to both the test subject and the person doing the study. At the present time there are no published data to indicate the superiority of this or any other available procedure for testing the sensitizing capacities of chemicals.

In establishing various procedures for prophetic testing for the current study, the following findings in my previous studies formed the basis for such techniques:

(a) In the original technique an initial one-, two-, three-, or seven-day patch test was followed in two weeks by a second test for forty-eight hours. If no reaction appeared, one- or two-day tests were made successively at weekly intervals until sensitization occurred. If results were negative after eight such treatments, a final seven-day test was made. The tests had been applied on the arm in a reverse S order, so that the sites were about 2 to 3 inches apart laterally or vertically. This technique rendered sensitive the greatest number of subjects, namely 87 per cent[1] to 90-plus per cent (extended series). It was felt that the proximity to each other of test exposures was the factor of consequence in establishing sensitization by this procedure.

(b) A much simpler procedure consisted of a single seven-day patch test. This was effective in sensitizing twenty-one of twenty-nine subjects, or 72 per cent.[3] The incubation period in this group ranged from nine to fourteen days, indicating that excitant or related reacting substance could remain fixed in the skin for at least fourteen days after a single contact with the skin.

TABLE I. PLAN OF PROCEDURES FOR PROPHETIC TESTING

DAYS	1 | 2 | 3 | 4 | 5 | 6 | 7	8 | 9 | 10 | 11 | 12 | 13 | 14	15 | 16 | 17 | 18 | 19 | 20 | 21	22 | 23 | 24 | 25 | 26 | 27 | 28	29 | 30 | 31 | 32 | 33 | 34 | 35	36 | 37
A	Left arm Right arm		Right arm		Left arm	
B	Left arm Right arm		Left scapular area Right scapular area		Left arm	
C	Left arm Site 1	Site 2	Site 3	Site 4		R. arm
D	Left arm	Right arm	Left scapular area	Right scapular area	Left arm	
E	Forearm L R L Arm	Subclavicular area R L R	Scapular area L R L Thigh	R		Arm L

(c) In reviewing the findings of the spontaneous flare reaction[2] in subjects sensitized by multiple successively applied patch tests to sites close to each other, it was evident that as many as three previously nonreacting sites could flare up. Moreover, some of the sites which reacted had been treated as long as forty-two days previously, indicating that excitant or related reacting substance could remain fixed in the skin for as long as seven weeks.

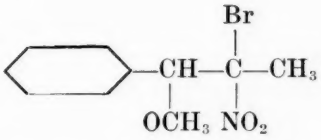
(d) Where spontaneous flare-up of more than one treated site took place, this phenomenon occurred in the reverse order to that in which these sites had been treated. Further, it was demonstrated that this order of flare-up was related to the concentration and/or amount of residual antigen remaining at the respective reacting sites. It seemed reasonable to infer that each successive application to the skin influenced the immunologic processes which were developing, and that the final outcome or state of hypersensitiveness was a summation of the individual stimuli made by the successive patch test contacts of the skin with the excitant.

PROCEDURES

In planning the procedures for the present study, the site locations were varied so that patch tests were applied close to each other or at great distances from each other. Exposure time was also varied, tests being applied for one-, two-, three-, four-, and seven-day periods, with the total testing time ranging from thirty-one to thirty-eight days. The usual incubationary period for establishing eczematous sensitization was thus adequately provided for.

Four different procedures were devised. Eventually the findings obtained by each procedure were to be compared with each other and with the procedure recommended by Draize.

The chemical used for testing* was 2-nitro-2 bromo-1 methoxy-1-phenyl-propane



which, by preliminary study, was found to be capable of sensitizing the human skin. It was employed in 1 per cent concentration in a water-soluble ointment base. Control testing with the ointment for one- to two-day periods indicated that the chemical in this concentration was not a primary irritant to the skin. One and five per cent solutions of the chemical in mineral oil were also used to determine whether sensitivity had been induced.

The testing procedures will be referred to as *A,B,C,D,* and *E,* the last being that suggested by Draize (Table I).

*Furnished by Dr. Michael G. Mulinos, Medical Director, Commercial Solvents Corporation.

Procedure A:

1. Patch test applications to the lateral surfaces of both right and left arms, for a seven-day period; observation from the eighth to fourteenth days, inclusive.
2. Patch test application to an untreated area of the right arm for seven days; observation from the twenty-second to twenty-eighth days, inclusive.
3. Patch test on the lateral surface of the left arm for a forty-eight-hour period, to determine whether sensitivity was present.

Procedure B:

1. Patch test applications to both left and right arms for a four-day period; observation from the fifth to fourteenth days, inclusive.
2. Patch test applications to both left and right scapular or subclavicular areas for four days; observation from the nineteenth to twenty-eighth days, inclusive.
3. Patch test as in procedure *A*, step 3.

Procedure C:

This procedure is similar to that used originally by me[1] and discussed in the introduction. There were fewer steps, however. Four sites were selected on the left arm, approximately 2 or 3 inches from each other, and arranged as follows: (1) (2)
(4) (3)

These sites were treated in the following manner:

1. Patch test to site (1) for three days; observation from the fourth to seventh days, inclusive.
2. Patch test to site (2) for two days; observation from the tenth to fourteenth days, inclusive.
3. Patch test to site (3) for two days; observation from the seventeenth to twenty-first days, inclusive.
4. Patch test to site (4) for seven days, observation from the twenty-ninth to thirty-fifth days, inclusive.
5. Patch test on the right arm, as in procedure *A*, step 3.

Procedure D:

This procedure is an attempt to shorten the Draize method. Only five tests were used, and the treatment days were changed from one to a three- or four-day period.

1. Patch test application to the left arm for four days; observation from the fifth to seventh days, inclusive.
2. Patch test application to the right arm for four days; observation from the twelfth to fourteenth days, inclusive.
3. Patch test application to the left scapular area for three days; observation from the eighteenth to twenty-first days, inclusive.

4. Patch test application to the right scapular area for three days; observation from the twenty-fifth to twenty-eighth days, inclusive.
5. Patch tests as in procedure *A*, step 3.

Procedure E:

This is the procedure recommended by Draize. Patch tests were applied for twenty-four hour periods on alternate days, three times a week, for a total of ten exposures. They were applied, successively, to the following areas: left then right mid-forearm, left then right arm, left then right subclavicular areas, left then right scapular areas, left then right lower thigh. A challenging twenty-four hour test was finally made on the upper left forearm two weeks after the tenth, or final, test application.

TECHNIQUE

The patch consisted of a ¾ inch (1.8 cm.) square pad made of multiple layers of gauze attached to a 1½ inch (3.8 cm.) square of waterproof adhesive tape. A cotton-tipped applicator was dipped into the ointment and the latter was then rubbed into the gauze pad until the gauze was thoroughly covered with the ointment. Then an area of skin, about the size of a dime, was thoroughly covered with the ointment, by moving the ointment-covered applicator tip in this area in a circular direction about eight to ten times. The patch was then applied over this area. Treatment of both skin and gauze pad in this manner assured intimate contact between skin and chemical during the period of treatment. For further protection of the treated site, the patch was sealed down with strips of waterproof plastic adhesive tape, overlapping the patch on all sides. The subjects were instructed not to shower or otherwise moisten the test patches while they were in situ.

For the final tests, the ointment was merely applied to the surface of the gauze pad. The skin was not treated with the ointment. Where the oily solution of the drug was used, it was applied to the gauze pad by glass rod until the pad was saturated. Tests were also sealed to the skin by means of the waterproof adhesive tape.

Final tests were generally made with the ointment, the base, and the 1 per cent solution in oil. As the study progressed, it was ascertained that the ointment base produced no irritation or reaction, and its use was discontinued. A 5 per cent oil solution was used at times as an additional test.

SUBJECTS

It had been planned that twenty-five subjects would be studied by each of the five methods. The final numbers of subjects who came to completion were twenty-six each in groups *A* and *E*, twenty-five each in groups *B* and *C*, and nineteen in group *D* (Table III).

The subjects were predominantly young men and women, there being ninety-two subjects below the age of 30 years (Table II). There were fifty-eight male and sixty-three female subjects. Two of the subjects had light-

colored skin. The subjects, for the most part, were volunteer college students. In addition, there were patients from the allergy clinic and parents of allergic patients.

All subjects were questioned for personal and family history of atopic diseases (hay fever, asthma, atopic dermatitis) and for a past history of poison ivy or other contact dermatitis. Forty-one subjects gave a positive personal history of atopic diseases, and forty-six had a positive family history of atopy.

TABLE II. (A) DISTRIBUTION OF SUBJECTS ACCORDING TO AGE AND SEX AND (B) SENSITIZED SUBJECTS ACCORDING TO AGE GROUPS

A			B	
AGE GROUPS (YEARS)	MALES	FEMALES	SUBJECTS SENSITIZED NUMBER	SUBJECTS SENSITIZED PER CENT
10 to 19	24	15	6	15
20 to 29	31	22	7	13
30 to 39	1	14	3	20
40 to 49	1	6	0	0
50 to 59	1	6	1	14

Twenty-nine subjects had had one or more attacks of plant dermatitis, mainly due to poison ivy. One subject had had a recurring atopic dermatitis and one had had a recurring urticaria, but these conditions were inactive at the time of the study.

FINDINGS AND DISCUSSION

Procedures.—The technique of application was uniform throughout the experiment. Generally the prescribed plans of testing were adhered to. There was an occasional unavoidable deviation caused by a subject's school program, holiday, illness, or other reason. The final conclusions could be influenced slightly, if at all, by these variations in procedure. Nevertheless, attention is called to these variations. Among group *A* subjects, the dual tests were made at the second application in two of them instead of at the first testing. In two other subjects, only single seven-day tests were done. In one subject, the second test had been omitted because of the subject's absence and, in another, because the skin showed an intense erythema upon removal of the initial tests.

TABLE III. SENSITIZED SUBJECTS ACCORDING TO PROCEDURE OF PROPHETIC TESTING

PROCEDURE	NUMBER OF SUBJECTS	SUBJECTS SENSITIZED NUMBER	SUBJECTS SENSITIZED PER CENT
Group A	26	5	19
Group B	25	1	4
Group C	25	8	32
Group D	19	2	10
Group E	26	1	4
Total	121	17	14

In group *B*, the dual tests were not done at the second application in one subject. In group *C*, three of the subjects had, in error, removed the final or fourth test after two days instead of seven days. Since this group yielded the highest percentage of sensitized subjects (Table III) and since the seven-day exposure is considered to be an important feature of procedure *C*, it is possible that one of the three subjects could have been sensitized.

Analysis of Subjects Sensitized.—A total of seventeen subjects became sensitized, representing 14 per cent of the total group of 121 subjects (Table III). According to the procedure used, there were five sensitized subjects in group *A* (19 per cent), one in group *B* (4 per cent), eight in group *C* (32 per cent), two in group *D* (10 per cent), and one in group *E* (4 per cent).

Six of the sensitized subjects gave a positive personal history and seven a positive family history of atopy (Table IV). Six subjects had had poison ivy dermatitis in the past. Of the two Negro subjects, C., W. of group *A*, became sensitized.

TABLE IV. SENSITIZED SUBJECTS (SUMMARY)

GROUP	SUBJECT	SEX	AGE	ATOPY		POISON IVY	TEST REACTIONS				DAY	SITE NO.
				PERSONAL HISTORY	FAMILY HISTORY		1% OINTMENT (DEGREES)	BASE	1% OIL (DEGREES)	5% OIL (DEGREES)		
A	C., W.	M	25	0	0	0	3*	0	0	3+	30	3
	F., L.	M	18	0	0	0	3	0	–	3+	37	3
	G., B.	F	20	0	0	+	3-4	0	3	–	24	2
	M., A.	M	17	0	0	0	3	0	2	3	23	2
	S., R.	M	18	0	0	+	3	0	0	3	30	3
B	U., R.	F	18	0	0	0	1-2	0	0	2	22	2
C	B., R.	F	51	+	+	+	2	0	–	2-3	44	5
	B., M.	F	29	+	+	+	2	0	–	1-2	44	5
	K., H.	M	24	+	+	0	3+	0	–	3	38	5
	K., M.	F	38	0	+	0	3-4	0	–	3	37	5
	L., C.	F	26	0	+	0	2-3	0	0	3	37	5
	L., F.	F	34	+	0	0	3	0	2-3	3-4	37	5
	M., R.	F	32	+	0	+	3	0	2-3	–	17	3
	S., E.	M	19	0	0	+	3	0	–	3	18	3
D	K., E.	M	21	0	0	0	2-3	0	–	3	36	5
	S., M.	M	18	0	+	0	2-3	0	–	3	32	5
E	R., M.	M	21	+	+	0	3	0	1-2	2	40	11

*Bloch standard.

According to age group (Table II) the following number of subjects became sensitized: six, or 15 per cent, between 10 and 19 years of age; seven, or 13 per cent, between 20 and 29 years; three, or 20 per cent, between 30 and 39 years; and one, or 14 per cent, between 50 and 59 years. There were nine male subjects and eight female subjects who reacted.

Reactions.—It was not uncommon, upon removal of the three- to seven-day patch tests, to find an erythema reaction which eventually went on to faint desquamation. These reactions resembled those elicited by tests with soap solutions. Control tests with the ointment base for twenty-four- to twenty-eight-hour periods were found to be entirely negative. These primary reactions were then considered to be due to the prolonged intimate contact of the chemical-ointment combination to the skin. A review of the forty-eight hour tests revealed that a one-plus erythema, which usually cleared after twenty-four hours, was due in five instances to the ointment and in two instances each to the 1 per cent and the 5 per cent oily solutions of the excitant.

The reactions which indicated that the subjects had become sensitized were very typical, presenting erythema, infiltration, papules, vesicles, and occasionally bullae. Marked itching was present. The sites remained active for several weeks, and pigmentation continued for a longer period. Most of the reactions were in the 3-degree (Bloch) range (Table IV). The strongest reactions were generally due to the 5 per cent oily solution. The ointment frequently gave a stronger reaction than the 1 per cent oily solution. Where the reaction to the ointment was stronger than that to the 5 per cent oily solution, it usually related to a seven-day test site; the 5 per cent solution never had been kept in situ for longer than two days.

The spontaneous flare-up phenomenon occurred in three subjects, once each in groups *A*, *D*, and *E*.

Comparison of Procedures.—The procedures of testing and their respective findings may be compared from the standpoint of technical facility, the period of study or observation, the intensity of reactions, and their frequency. In *A* and *B* there were three test sessions; there were five in procedures *C* and *D;* and eleven test sessions in *E*. In terms of efficacy, procedure *A* was the simplest of performance, with an incidence of sensitization of 19 per cent. The least convenient method, requiring eleven test sessions and yielding an incidence of sensitization of 4 per cent, was procedure *E*, the plan recommended by Draize. In terms of site exposure days, there were twenty-three, eighteen, sixteen, sixteen, and eleven days, respectively.

The period of study in procedures *A*, *B*, and *D* was thirty days, and in *C* and *E* it was thirty-seven days. The usual incubation period for sensitization was thus adequately provided for. The subjects were observed for these periods, and some were observed for longer periods. Sensitization occurred before the end of the planned period in five instances, namely, on the seventeenth to twenty-fourth days. Thus, in group *A*, a positive reaction appeared at the second test in two subjects; in group *B*, one subject reacted at the second test; and in group *C*, a positive reaction occurred at the third test in two subjects.

The strongest reactions seemed to occur in groups *A* and *C*, which yielded the highest incidence of reactions, 19 and 32 per cent, respectively. In both of these procedures the seven-day patch test was considered an essential step. Procedure *C*, moreover, differed from the others in that repeated insults had been made to closely approximated sites, thus concentrating the excitant in a small area. In all other procedures, the excitant had been spread out over widely separated areas of the body. Procedure *C* was, in principle, the same used by me in my original experiments with krameria, eight or nine steps having been employed then.

Evaluation of Study.—I am cognizant of the inadequacies of studying small groups of subjects for the purpose of statistical analysis, but studying human beings on an experimental level entails the problem of securing subjects, getting their full cooperation, arranging for frequent meetings with them at mutually satisfactory times, and other deterring factors.

I further recognize the following limitations of this study: (a) small groups of approximately twenty-five subjects each were used, (b) only one concentration of the chemical was employed, and (c) only one chemical substance was employed.

It becomes obvious, from a consideration of the various facets of the problem at hand, that the following factors need study by themselves and in combination with each other: the concentration of the excitant, the location and distribution of the sites, the frequency of application, and the exposure time or duration of application of the excitant. Only by expanded studies in larger numbers of subjects can these essentials be evaluated adequately in terms of the prescription of a system of testing. Nor can one hope, obviously, to devise a single procedure which would meet the requirements for all types of chemicals and for all manners of use on the skin to which they are to be put. The present study merely represents a small step in the direction of the solution of the problem at hand.

SUMMARY

This is a further study into the problem of factors involved in the mechanisms of sensitization of the human skin. In devising techniques of sensitization, such variations in procedure were recognized as (a) short and prolonged patch test exposures, (b) their frequency of application, (c) their total number, and (d) their distribution on various areas of the body. A chemical substance, heretofore not used on the human skin, was employed, and was found in preliminary observations to be able to sensitize the skin by percutaneous application.

Four variations in procedure (*A*, *B*, *C*, and *D*) were established, based on findings in previous experiments and studies in skin sensitization by myself and others. A fifth procedure (*E*), employed for purpose of comparison, was that suggested by the United States Food and Drug Administration for studying the sensitizing potentials of unknown chemicals.

The number of subjects studied was 121, approximately equal numbers being treated by each of the five procedures. Seventeen subjects, or 14 per cent of the total, became sensitized, the percentages in each group being *A*, 19 per cent; *B*, 4 per cent; *C*, 32 per cent; *D*, 10 per cent; and *E*, 4 per cent.

In comparing and evaluating the factors of location and distribution of patch test sites and of the exposure time or duration of application of the excitant, I believe that the effectiveness of procedure *C* in yielding the highest incidence of sensitization can be attributed to the prolonged (seven-day) patch test and to the distribution of the patch test sites over a small area of skin.

REFERENCES

1. Grolnick, M.: Studies in Contact Dermatitis. III. Active Sensitization With Krameria in Man, J. Invest. Dermat. **1**: 179, 1938.
2. Grolnick, M.: Studies in Contact Dermatitis. IV. The Spontaneous Flare-Up of Negative Test Sites in Experimental Sensitization in Man, J. Immunol. **41**: 127, 1941.
3. Grolnick, M.: Contact Allergy of the Skin, Ann. New York Acad. Sc. **50**: 718, 1949.

4. Sulzberger, M. B., and Simon, F. A.: Arsphenamine Hypersensitiveness in Guinea Pigs. III. Experiments Demonstrating (A) The Regional Geographic Variability in Susceptibility to Sensitization; (B) The Chemical Specificity of the Hypersensitivity; and (C) The Variation in Sensitizing Proclivities (Sensitization Index) of Different Brands, J. ALLERGY **6**: 39, 1934.
5. Rostenberg, A., Jr., and Sulzberger, M. B.: Some Results of Patch Tests, Arch. Dermat. & Syph. **35**: 433, 1937.
6. Rostenberg, A., Jr., and Kanof, N. M.: Studies in Eczematous Sensitization. 1. A Comparison Between the Sensitizing Capacities of Two Allergens and Between Two Different Strengths of the Same Allergens, and the Effect of Repeating the Sensitizer Dose, J. Invest. Dermat. **4**: 505, 1941.
7. Schwartz, L., et al.: Outbreak of Dermatitis From New Resin Fabric Finishes, J.A.M.A. **115**: 906, 1940.
8. Schwartz, L.: Dermatitis From New Synthetic Resin Fabric Finishes, J. Invest. Dermat. **4**: 459, 1941.
9. Schwartz, L., and Peck, S. M.: Cosmetic Dermatitis, New York, 1946, Paul B. Hoeber, Inc., p. 151.
10. Straus, H. W.: Studies in Experimental Hypersensitiveness in the Rhesus Monkey. I. Active Sensitization With Poison Ivy, J. Immunol. **32**: 241, 1937.
11. Wedroff, N. S., and Dolgoff, A. D.: Concerning the Specific Sensitivity of Skin Due to Simple Chemical Compounds, Arch. Dermat. u. Syph. **171**: 647, 1935.
12. Draize, J. H., Woodward, G., and Calvery, H. O.: Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes, J. Pharmacol. & Exper. Therap. **82**: 377, 1944.
13. Draize, John H.: Personal communication.

American Academy of Allergy

Annual Meeting—Feb. 6, 7, and 8, 1956
Postgraduate Review—Feb. 4 and 5, 1956
Chase-Park Plaza Hotels
St. Louis, Missouri

PROGRAM

The Scientific Session of the annual meeting, to be held all day Monday, all day Tuesday, and Wednesday morning, Feb. 6, 7, and 8, 1956, will be comprised of original presentations of clinical and investigative studies by members and fellows of the Academy. Distinguished guest speakers who will address the Academy on each day of the Scientific Session on subjects of foremost interest to allergists include the following:

"The Gamma Globulins." Charles A. Janeway, M.D., Thomas Morgan Rotch Professor of Pediatrics, Harvard University School of Medicine, and Physician-in-Chief, Children's Hospital, Boston, Massachusetts.

"Bacterial Hypersensitivity." Sidney Raffel, M.D., Professor of Bacteriology, Stanford University School of Medicine, Stanford, California.

"Immunohematology." Carl V. Moore, M.D., Busch Professor of Medicine, Chairman of Department of Medicine, Washington University School of Medicine, and Physician-in-Chief, Barnes Hospital, St. Louis, Missouri.

"Pathogenesis of Allergic Contact Dermatitis." Herman N. Eisen, M.D., Professor of Medicine and Director of Dermatology Section, Washington University School of Medicine, St. Louis, Missouri.

"Allergy and the Food and Drug Administration." Irvin Kerlan, M.D., Associate Medical Director and Chief, Research and Reference Branch, Division of Medicine, Department of Health, Education and Welfare, Food and Drug Administration, Washington, D. C.

The Postgraduate Review will be comprised of three panels to be held Saturday morning, February 4, Saturday afternoon, February 4, and Sunday afternoon, February 5, on the following subjects:

"Immunological and Clinical Aspects of Antigen Therapy." Moderator, Oscar Swineford, Jr., M.D., Professor of Internal Medicine (Allergy-Arthritis Division), University of Virginia School of Medicine, Charlottesville, Virginia.

"Indications and Contraindications in the Treatment of Asthma." Moderator, Leo H. Criep, M.D., Associate Professor of Medicine and Chief of Allergy Clinic, Pittsburgh University School of Medicine, Pittsburgh, Pennsylvania.

"The Allergic Child." Moderator, Charles A. Janeway, M.D. (see above).

The 1956 meeting of the Association of Allergists for Mycological Investigations is tentatively set for Sunday morning, Feb. 5, 1956, at the Chase-Park Plaza Hotels, St. Louis, Missouri.

The final program of the Postgraduate Review and the Scientific Session of the annual meeting will be published in the January, 1956, issue of the JOURNAL OF ALLERGY.

Each subscriber to the JOURNAL OF ALLERGY, in addition to the membership of the Academy, will be mailed a copy of the final program in the month of December, 1955.

The Program Committee:

W. B. Sherman, M.D.
S. C. Bukantz, M.D.
K. P. Mathews, M.D.
S. F. Hampton, M.D., Chairman.

Announcements

Fourth International Congress of Internal Medicine

The Fourth International Congress of Internal Medicine will be held in Madrid, Sept. 19 to 23, 1956, under the Presidency of Prof. C. Jiménez Díaz.

There will be two main subjects: "The Role of the Adrenals in the Pathogenesis and Evolution of Internal Diseases" and "Bronchial Asthma and Emphysema," each of which will be dealt with by a number of speakers. Communications on these themes or on any others of free choice will also be admitted.

Please address all inquiries to the Secretariat: Doctors J. C. de Oya and J. Gimena, Hortaleza n° 90, Madrid, Spain.

The Eleventh International Congress of Dermatology

The Eleventh International Congress of Dermatology will be held in Stockholm, July 31 to Aug. 5, 1957. The honorary president is Prof. Guido Miescher, Zürich; the president is Prof. Sven Hellerström, M.D.; and the secretary general is C. H. Flodén, M.D.

Papers and discussions will be held in English, French, German, and Spanish. A preliminary program will be distributed late in 1955. The secretary may be addressed at Hudkliniken, Karolinska sjukhuset, Stockholm 60, Sweden.

Allergy Foundation of Northern California

Newly elected officers of the Allergy Foundation of Northern California, Inc., are: chairman of the board of governors, Dr. M. Coleman Harris, San Francisco; vice-chairman, Dr. Grace Talbott, San Francisco; and secretary-treasurer, Dr. Albert Rowe, Jr., Oakland.

The Foundation announces that during the ensuing twenty-four months a field survey of the San Francisco Bay area and surrounding counties will be carried out by Mr. McMinn, botanist of Mills College, Oakland, California. A survey will be made of pollen-producing plants in the area. The results of the survey, including photographs, will be published at its completion.

Award to Dr. Bret Ratner

At an open meeting of the Section on Allergy of the American Academy of Pediatrics, held at the Palmer House in Chicago, Illinois, on Oct. 3, 1955, a scroll was presented to Dr. Bret Ratner of New York City by Dr. Jerome Glaser of Rochester, New York, chairman, in behalf of the Section. The scroll reads as follows:

"By unanimous vote of the Section on Allergy of the American Academy of Pediatrics assembled in Chicago at the Twenty-Third annual meeting of the academy, this scroll is awarded to Bret Ratner, M.D., as an expression of gratitude and appreciation for his untiring services in advancing pediatric allergy:

"As a pioneer investigator and teacher.

"As organizer of the Section on Allergy and as its first chairman.

"For his successful efforts in obtaining recognition by certification for pediatric allergists in the sub-specialty of pediatric allergy."

Residencies in Allergy

A residency in allergy is available at United States Veterans Hospital (North Side), Chicago. This residency combines the Veterans Hospital service together with the facilities in allergy at Northwestern University Medical School, and is approved by the Board of Internal Medicine and the subspecialty Board of Allergy. For further information, write to Dr. Samuel M. Feinberg, 303 E. Chicago Ave., Chicago 11, Illinois.

Applications are being received for an approved residency in allergy at the United States Veteran's Hospital and at the Medical Center, University of Pittsburgh, School of Medicine, for the year beginning July 1, 1956. Please address inquiries to Leo H. Criep, M.D., The Bigelow, Pittsburgh 19, Pennsylvania.

AUTHORS INDEX*

A

ALEXANDER, HARRY L. (*See* FRANKEL, JOHNSON, SCHIELE, BUKANTZ, AND ALEXANDER), 33

ALVAREZ, JOSE CADRECHA, AND CASTRO, JAVIER FERNANDEZ. Numbers and kinds of air-borne, culturable fungus spores in Havana, Cuba, 150

ARBESMAN, CARL E. Clinical studies in allergy with several new drugs, 87 (Abst.)

—. Report of Committee on Drugs of the Research Council of the American Academy of Allergy, 1954-1955, 377

— AND EHRENREICH, ROBERT J. Meticorten and 9 alpha fluorohydrocortisone in the treatment of allergic disorders, 189

—, TERPLAN, KORNEL L., NETER, ERWIN, AND BERTRAM, LEE F. The effects of ACTH and cortisone on the pathology of reversed anaphylaxis in the guinea pig, 123

ARNOLD, L. (*See* SIEGAL, GOLDMAN, ARNOLD, AND HERSCHBERGER), 80

ARONOW, SAUL. (*See* WANG, BURRAGE, IRWIN, AND ARONOW), 448

B

BALDWIN, HORACE, DEGARA, PAUL F., SPIELMAN, AARON D., AND DWORETZKY, MURRAY. ACTH and cortisone in the treatment of asthma, 44

BANCROFT, HULDAH. (*See* OGDEN, BANCROFT, RULI, STEPHENS, AND BRANSON), 78

BARUCH, DOROTHY W. (*See* MILLER AND BARUCH), 54

BATTISTO, J. R. (*See* CHASE AND BATTISTO), 83

BENAIM, C. (*See* STERNBERGER, FEINBERG, FEINBERG, BENAIM, AND WARREN), 82

—, FEINBERG, SAMUEL M., AND STERNBERGER, LUDWIG A. "Stresses" and hypersensitivity, 481

—, —, WARREN, S. A., AND STERNBERGER, L. A. The effect of adrenalectomy in the guinea pig on asthma from antigen aerosol and on its inhibition by nonspecific procedures, 86 (Abst.)

BERGER, KENNETH W. (*See* SWINEFORD, CUMBIA, BERGER, AND COLEMAN), 91

—. (*See* SWINEFORD, CUMBIA, BERGER, AND LUCAS), 305

BERNSTEIN, JEROME. (*See* SKAGGS, BERNSTEIN, AND COOKE), 201

BERRYMAN, GEORGE H. Cerebrospinal rhinorrhea simulating allergic rhinitis, 71

BERTRAM, LEE F. (*See* ARBESMAN, TERPLAN, NETER, AND BERTRAM), 123

BEST, C. A. (*See* COLLINS-WILLIAMS AND BEST), 461, 468

BLUE, JOHNNY A. Folklore remedy (Canada fleabane) for soybean diarrhea, 425

BOWEN, RALPH. Gamma-globulin and the asthmatic child, 87 (Abst.)

BRAND, ALTA. (*See* NOAH AND BRAND), 84, 385

BRANSON, CECIL. (*See* OGDEN, BANCROFT, RULI, STEPHENS, AND BRANSON), 78

BUKANTZ, SAMUEL C. (*See* FRANKEL, JOHNSON, SCHIELE, BUKANTZ, AND ALEXANDER), 33

— AND SCHIELE, ALINE W. Preliminary observations on the chemical nature of asthmatic sputum, 85 (Abst.)

BURRAGE, WALTER S. (*See* WANG, BURRAGE, IRWIN, AND ARONOW), 448

—, WANG, DAVID M. K., AND IRWIN, JOHN W. Cortisone or hydrocortisone in the treatment of severe, intractable bronchial asthma? 79 (Abst.)

C

CANDER, LEON, AND COMROE, J. H., JR. A method for the objective evaluation of bronchodilator drugs, 210

CASON, LOUISE R. Fungus colony counts from air-borne spores in Birmingham, Alabama, 367

CASTRO, JAVIER FERNANDEZ. (*See* ALVAREZ AND CASTRO), 150

CAVELTI, PHILIP A. Autoimmunologic disease, 95

CHAPIN, H. BEECHER. (*See* ROY, CHAPIN, AND FAVRE), 490

CHASE, M. W., AND BATTISTO, J. R. The duration of dermal sensitization following cellular transfer in guinea pigs, 83 (Abst.)

—, DAMESHEK, WILLIAM, HABERMAN, SOL, SAMTER, MAX, AND SQUIER, THEODORE L. The role of the formed elements of the blood in allergy and hypersensitivity (a symposium), 219

*Abstracts of papers presented at the American Academy of Allergy meeting are marked (Abst.).

COLEMAN, MONROE. (*See* SIEGEL, COLEMAN, WEISSMAN, AND SHER), 78
— AND SIEGEL, BERNARD B. Studies in penicillin hypersensitivity. II. The significance of penicillin as a contaminant, 253
COLEMAN, WILLIAM P. (*See* SWINEFORD, CUMBIA, BERGER, AND COLEMAN), 91
COLLINS-WILLIAMS, C., AND BEST, C. A. Atmospheric mold counts in Toronto, Canada, 468
— AND —. Atmospheric pollen counts in Toronto, Canada, 461
COMROE, J. H., JR. (*See* CANDER AND COMROE), 210
COOKE, ROBERT A. (*See* SKAGGS, BERNSTEIN, AND COOKE), 201
CRAWFORD, LLOYD V. (*See* RATNER AND CRAWFORD), 91, 320
CREPEA, S. B. Spontaneous pneumothorax complicating asthma, 88 (Abst.)
—. The significance of thickened basement membrane in the bronchial tree, 80 (Abst.)
— AND HARMAN, JOHN W. The pathology of bronchial asthma. I. The significance of membrane changes in asthmatic and non-allergic pulmonary disease, 453
CRIEP, LEO H., SCHEPARTZ, A. I., AND LEVINE, MACY. The serum electrophoretic pattern in experimental hypersensitivity in rabbits, 85 (Abst.)
—, —, —, AND TOTTEN, ROBERT S. Serum electrophoretic pattern in experimental hypersensitivity, 519
CRYST, SYDENHAM. (*See* GURNEY AND CRYST), 84, 533
CUMBIA, JESSE W. (*See* SWINEFORD, CUMBIA, BERGER, AND COLEMAN), 91
—. (*See* SWINEFORD, CUMBIA, BERGER, AND LUCAS), 305

D

DAMESHIEK, WILLIAM. (*See* CHASE, DAMESHEK, HABERMAN, SAMTER, AND SQUIER), 219
DEGARA, PAUL F. (*See* BALDWIN, DEGARA, SPIELMAN, AND DWORETZKY), 44
DINGLE, A. NELSON. A meteorologic approach to the hay fever problem, 297
DRAGSTEDT, CARL A. Histamine: its pharmacology and role in anaphylaxis, 287
DWORETZKY, MURRAY. (*See* BALDWIN, DE GARA, SPIELMAN, AND DWORETZKY), 44

E

EHRENREICH, ROBERT J. (*See* ARBESMAN AND EHRENREICH), 189
ELEGANT, LAWRENCE (*See* MATHESON AND ELEGANT), 415
ESSELLIER, A. F., JEANNERET, P., MARTI, H. R., AND ROSENMUND, H. Allergens in vegetable oils, 107
ETTELSON, LAWRENCE N., AND TUFT, LOUIS. Allergy to citric acid—case report and clinical study, 88 (Abst.)

F

FAVRE, JEAN. (*See* ROY, CHAPIN, AND FAVRE), 490
FEINBERG, A. R. (*See* STERNBERGER, FEINBERG, FEINBERG, BENAIM, AND WARREN), 82
FEINBERG, RICHARD J. (*See* FLICK AND FEINBERG), 262
FEINBERG, SAMUEL M. (*See* BENAIM, FEINBERG, AND STERNBERGER), 481
—. (*See* BENAIM, FEINBERG, WARREN, AND STERNBERGER), 86
—. (*See* STERNBERGER, FEINBERG, FEINBERG, BENAIM, AND WARREN), 82
— AND STERNBERGER, L. A. Action of histamine liberator compound 48/80 in the guinea pig, with a review of previous reports of its action in other species, 170
FLICK, JOHN A., AND FEINBERG, RICHARD J. The activity of human reagins exposed to the disinfectant, Beta-propiolactone, 262
FOLLENSBY, EDNA M. (*See* LOWELL, FRANKLIN, SCHILLER, AND FOLLENSBY), 86
—, LOWELL, FRANCIS C., AND SCHILLER, IRVING W. Studies on the source of the house dust antigen, 80 (Abst.)
FORSYTHE, WARREN E. (*See* MATHEWS, HEMPHILL, SHELDON, LOVELL, AND FORSYTHE), 78
FRANKEL, SAM. (*See* HAMPTON, JOHNSON, FRANKEL, AND SCHIELE), 16
—, JOHNSON, MARY C., SCHIELE, ALINE W., BUKANTZ, SAMUEL C., AND ALEXANDER, HARRY L. Fractionation of pollen extracts. II. Chemical and paper chromatographic investigation of ragweed pollen extracts, 33
FRANKLIN, WILLIAM. (*See* LOWELL, FRANKLIN, SCHILLER, AND FOLLENSBY), 86
—. (*See* SCHILLER, LOWELL, LYNCH, AND FRANKLIN), 11
FRAYSER, LOIS. Aeroallergins in Seattle, 88 (Abst.)
FYLES, T. W. (*See* ROSE, FYLES, AND SEHON), 86
—. (*See* ROSE, FYLES, AND VENNING), 1
—. (*See* SEHON, FYLES, AND ROSE), 329
—, PARE, J. A. P., AND ROSE, BRAM. The effect of corticotropin and cortisone on respiratory function in bronchial asthma, 340

G

GAILLARD, G. EVERETT. Clinical evaluation of a new antihistamine, buclizine hydrochloride (Vibazine), 373
GILCHRIST, MARY. (*See* WANG, BURRAGE, IRWIN, AND ARONOW), 448
GOLDMAN, J. L. (*See* SIEGAL, GOLDMAN, ARNOLD, AND HERSCHBERGER), 80

GORDON, PRISCILLA. (*See* WANG, BURRAGE, IRWIN, AND ARONOW), 448
GREGORY, DONALD. (*See* TUFT AND GREGORY), 92
—. (*See* TUFT, GREGORY, AND GREGORY), 92
—. (*See* TUFT, HECK, AND GREGORY), 359
GREGORY, JOAN. (*See* TUFT, GREGORY AND GREGORY), 92
GROLNICK, MAX. Sensitization of the human skin, 542
—. Sensitization of the human skin: a study of location of sites and exposure time of excitant, 83 (Abst.)
GURNEY, CLIFFORD W., AND CRYST, SYDENHAM. Aeroallergen studies with the molecular filter membrane, 533
— AND —. Studies on aeroallergens, 84 (Abst.)

H

HABERMAN, SOL. (*See* CHASE, DAMESHEK, HABERMAN, SAMTER, AND SQUIER), 219
HAMPTON, STANLEY F. (*See* JOHNSON, SCHIELE, AND HAMPTON), 89, 429
—, JOHNSON, MARY C., FRANKEL, SAM, AND SCHIELE, ALINE W. The preparation of highly concentrated allergenic extracts by increasing the concentration of extraction. I. Timothy and low ragweed pollens, 16
HARMAN, JOHN W. (*See* CREPEA AND HARMAN), 453
HECK, V. MURIEL. (*See* TUFT AND HECK), 59
—. (*See* TUFT, HECK, AND GREGORY), 359
HEMPHILL, FAY M. (*See* MATHEWS, HEMPHILL, SHELDON, LOVELL, AND FORSYTHE), 78
HERSCHBERGER, C. (*See* SIEGAL, GOLDMAN, ARNOLD, AND HERSCHBERGER), 80
HOWARD, WILLIAM ALLEN. Childhood complications of respiratory allergies, 88 (Abst.)
HOWES, HOMER A. Historian's report, American Academy of Allergy, Feb. 7, 1955, 283

I

IRWIN, JOHN W. (*See* BURRAGE, WANG, AND IRWIN), 79
—. (*See* WANG, BURRAGE, IRWIN, AND ARONOW), 448

J

JEANNERET, P. (*See* ESSELLIER, JEANNERET, MARTI, AND ROSENMUND), 107
JOHNSON, MARY C. (*See* FRANKEL, JOHNSON, SCHIELE, BUKANTZ, AND ALEXANDER), 33
—. (*See* HAMPTON, JOHNSON, FRANKEL, AND SCHIELE), 16
—, SCHIELE, ALINE W., AND HAMPTON, STANLEY F. Studies on the optimum concentration of glycerine in the preparation and preservation of ragweed pollen extract, 89 (Abst.); 429

K

KEENEY, EDMUND L., WEISS, HARRY A., AND MOHR, CHARLES F. The use of cortisone or ACTH during rapid desensitization of allergic patients, 141
KIND, S. L. Effect of the histamine liberator 48/80 in histamine-sensitive mice, 507
KNAPP, PETER H., AND MICHELSON, ALAN. Psychiatric, pulmonary, and adrenocortical observations in bronchial asthma, 80 (Abst.)

L

LEVINE, MACY. (*See* CRIEP, SCHEPARTZ, AND LEVINE), 85
—. (*See* CRIEP, SCHEPARTZ, LEVINE, AND TOTTEN), 519
LOVELL, ROBERT G. (*See* MATHEWS, HEMPHILL, SHELDON, LOVELL, AND FORSYTHE), 78
—, MATHEWS, KENNETH P., AND SHELDON, JOHN M. Dermatitis venenata from tree pollen oils—a clinical report, 89 (Abst.); 408
—, SHELDON, JOHN M., AND MATHEWS, KENNETH P. Observations on blood volume in patients in status asthmaticus and during a normal period, 90 (Abst.)
LOWELL, FRANCIS C. (*See* FOLLENSBY, LOWELL, AND SCHILLER), 80
—. (*See* SCHILLER, LOWELL, LYNCH, AND FRANKLIN), 11
—, FRANKLIN, WILLIAM, SCHILLER, IRVING W., AND FOLLENSBY, EDNA M. Observations on the intravenous injection of allergenic extracts in patients with hay fever and asthma, 86 (Abst.)
—, SCHILLER, IRVING W., AND LYNCH, MARY T. Estimation of daily changes in the severity of bronchial asthma, 113
LUCAS, DAVIS C. (*See* SWINEFORD AND LUCAS), 91
—. (*See* SWINEFORD, CUMBIA, BERGER, AND LUCAS), 305
LYNCH, MARY T. (*See* LOWELL, SCHILLER, AND LYNCH), 113
—. (*See* SCHILLER, LOWELL, LYNCH, AND FRANKLIN), 11

Mc

MCINTIRE, FLOYD C. The quantitative determination of histamine in animal tissues, 292

M

MAIETTA, ANGELO L. Metrorrhagia, an uncommon symptom of a constitutional reaction, 90 (Abst.)

MARTI, H. R. (*See* ESSELLIER, JEANNERET, MARTI, AND ROSENMUND), 107

MATHESON, ABE, AND ELEGANT, LAWRENCE. Penicillin reactions in children, 415

MATHEWS, KENNETH P. (*See* LOVELL, MATHEWS, AND SHELDON), 89, 408

—. (*See* LOVELL, SHELDON, AND MATHEWS), 90

—, HEMPHILL, FAY M., SHELDON, JOHN M., LOVELL, ROBERT G., AND FORSYTHE, WARREN E. A controlled study on the use of parenteral and oral antihistamines in preventing penicillin reactions, 78 (Abst.)

MAYER, R. L. Shortcomings of the experimental methods for detection of sensitizing properties of new drugs, 133

MERKSAMER, DAVID, AND SHERMAN, HYMAN. An evaluation of molds as an allergenic factor in the New York metropolitan area. A seven-year study, 81 (Abst.)

MICHELSON, ALAN. (*See* KNAPP AND MICHELSON), 80

MILLER, HYMAN, AND BARUCH, DOROTHY W. Bronchial asthma unrelated to positive skin reactions, 54

MOHR, CHARLES F. (*See* KEENEY, WEISS, AND MOHR), 141

MOTLEY, ATWELL. (*See* SWINEFORD AND MOTLEY), 91

N

NETER, ERWIN. (*See* ARBESMAN, TERPLAN, NETER, AND BERTRAM), 123

NOAH, JOSEPH W., AND BRAND, ALTA. Correlation of blood histamine release and skin test response to multiple antigens, 84 (Abst.); 385

O

OGDEN, HENRY D., BANCROFT, HULDAH, RULI, JACK, STEPHENS, WILLIAM, AND BRANSON, CECIL. Nasal hydrocortisone in allergic rhinitis: a controlled study, 78 (Abst.)

P

PARE, J. A. P. (*See* FYLES, PARE, AND ROSE), 340

PASSENGER, RICHARD E., SPAIN, W. C., AND STRAUSS, MARGARET B. Experience with Aqua Ivy: treatment of sensitive patients and toxicity studies on the guinea pig, 90 (Abst.)

PERLMAN, ELY. Further studies on the fractionation of ragweed pollen extracts, 86 (Abst.)

PRINCE, HOMER E. A dilemma in allergy, 279

R

RAPPAPORT, BEN Z. The histologic and histochemical changes in atopic dermatitis. I., 82 (Abst.)

—. The histologic and histochemical changes in atopic dermatitis following corticoid therapy. II., 82 (Abst.)

RASMUSSEN, HOWARD. Iodide sensitivity in the etiology of periarteritis nodosa, 81 (Abst.); 394

RATNER, BRET, AND CRAWFORD, LLOYD V. Allergenicity of modified processed foodstuffs. VII. Gelatin: anaphylactogenic properties of gelatin and its precursors, 91 (Abst.); 320

ROSE, BRAM. (*See* FYLES, PARE, AND ROSE), 340

—. (*See* SEHON, FYLES, AND ROSE), 329

—. Corticotrophin, cortisone, and hydrocortone therapy in asthma in relation to hyperglycemia and diabetes mellitus, 79 (Abst.)

—, FYLES, T. W., AND SEHON, A. A. Electrophoretic separation of skin-sensitizing antibody from ragweed-sensitive patients, 86 (Abst.)

—, —, AND VENNING, E. H. Corticotrophin, cortisone, and hydrocortisone in diseases of hypersensitivity. I. Biological corticoid excretion during acute symptoms, 1

ROSENMUND, H. (*See* ESSELLIER, JEANNERET, MARTI, AND ROSENMUND), 107

ROY, JEAN, CHAPIN, H. BEECHER, AND FAVRE, JEAN. Studies in pulmonary ventilatory function. I. Vital capacity, first one-second capacity, and forced respiratory curves in patients with asthma: comparative evaluation of methods, 490

RULI, JACK. (*See* OGDEN, BANCROFT, RULI, STEPHENS, AND BRANSON), 78

S

SAMTER, MAX. (*See* CHASE, DAMESHEK, HABERMAN, SAMTER, AND SQUIER), 219

—. Report of Research Council of the American Academy of Allergy, 474

SANTOS, I. N. (*See* UNGER AND SANTOS), 92

SCHEPARTZ, A. I. (*See* CRIEP, SCHEPARTZ, AND LEVINE), 85

—. (*See* CRIEP, SCHEPARTZ, LEVINE, AND TOTTEN), 519

SCHIELE, ALINE W. (*See* BUKANTZ AND SCHIELE), 85

—. (*See* FRANKEL, JOHNSON, SCHIELE, BUKANTZ, AND ALEXANDER), 33

—. (*See* HAMPTON, JOHNSON, FRANKEL, AND SCHIELE), 16

—. (*See* JOHNSON, SCHIELE, AND HAMPTON), 89, 429

SCHILLER, IRVING W. (*See* FOLLENSBY, LOWELL, AND SCHILLER), 80

—. (*See* LOWELL, FRANKLIN, SCHILLER, AND FOLLENSBY), 86

—. (*See* LOWELL, SCHILLER, AND LYNCH), 113
—, LOWELL, FRANCIS C., LYNCH, MARY T., AND FRANKLIN, WILLIAM. The effect of helium-oxygen mixtures on pulmonary function in asthmatic patients, 11
SCHWARTZ, EMANUEL. Metacortandracin (prednisone) in bronchial asthma, 206
SEHON, A. A. (*See* ROSE, FYLES, AND SEHON), 86
—, FYLES, T. W., AND ROSE, BRAM. Electrophoretic separation of skin-sensitizing antibody from the sera of ragweed-sensitive patients, 329
SHELDON, JOHN M. (*See* LOVELL, MATHEWS, AND SHELDON), 89, 408
—. (*See* LOVELL, SHELDON, AND MATHEWS), 90
—. (*See* MATHEWS, HEMPHILL, SHELDON, LOVELL, AND FORSYTHE), 78
—. Undergraduate medical education in allergy (president's address, American Academy of Allergy, Feb. 7, 1955), 275
SHER, MERLE. (*See* SIEGEL, COLEMAN, WEISSMAN, AND SHER), 78
SHERMAN, HYMAN. (*See* MERKSAMER AND SHERMAN), 81
SIEGAL, S., GOLDMAN, J. L., ARNOLD, L., AND HERSCHBERGER, C. Sinus disease, bacterial allergy and bronchial asthma, 80 (Abst.)
SIEGEL, BERNARD B. (*See* COLEMAN AND SIEGEL), 253
—, COLEMAN, MONROE, WEISSMAN, LESTER, AND SHER, MERLE. Studies in penicillin hypersensitivity. I. Immunologic nndings in two penicillin sensitive patients, 78 (Abst.)
SILVETTE, HERBERT, SWINEFORD, OSCAR, JR., AND TULL, LOUISE. Observations on acacia as an immunizing, sensitizing anaphylactogenic, and desensitizing antigen, 509
SKAGGS, JOSEPH T., BERNSTEIN, JEROME, AND COOKE, ROBERT A. Metacortandracin in chronic asthma, 201
SPAIN, W. C. (*See* PASSENGER, SPAIN, AND STRAUSS), 90
—. (*See* STRAUSS AND SPAIN), 471
SPIELMAN, AARON D. (*See* BALDWIN, DE GARA, SPIELMAN, AND DWORETZKY), 44
SQUIER, THEODORE L. (*See* CHASE, DAMESHEK, HABERMAN, SAMTER, AND SQUIER), 219
STEPHENS, WILLIAM. (*See* OGDEN, BANCROFT, RULI, STEPHENS, AND BRANSON), 78
STERN, P. Interpretation of the inefficacy of antihistaminics upon the secretion of gastric juices, 268
STERNBERGER, LUDWIG A. (*See* BENAIM, FEINBERG, AND STERNBERGER), 481
—. (*See* BENAIM, FEINBERG, WARREN, AND STERNBERGER), 86
—. (*See* FEINBERG AND STERNBERGER), 170
—, FEINBERG, A. R., FEINBERG, S. M., BENAIM, C., AND WARREN, S. A. A fibrocrystalloid antigen from alternaria, 82 (Abst.)
STRAUSS, MARGARET B. (*See* PASSENGER, SPAIN, AND STRAUSS), 90
— AND SPAIN, W. C. A new micro Seitz type filter, 471
SWINEFORD, OSCAR, JR. (*See* SILVETTE, SWINEFORD, AND TULL), 509
— AND LUCAS, DAVIS C. Treatment of pollen hay fever and asthma with aerosols of pollen extracts; introductory observations, 91 (Abst.)
— AND MOTLEY, ATWELL. Prevention or amelioration of reactions to specific aerosols of antigens by pretreatment with aerosols of antihistamines and sympathomimetics, 91 (Abst.)
— AND TULL, LOUISE. Arthus desensitization, 83 (Abst.)
—, CUMBIA, JESSE W., BERGER, KENNETH W., AND COLEMAN, WILLIAM P. The asthmagram: cases illustrating its use, 91 (Abst.)
—, —, —, AND LUCAS, DAVIS C. Treatment of pollen hay fever and asthma with aerosols of pollen extracts, 305
—, TULL, LOUISE N., AND WESTERVELT, F. B., JR. Studies in bacterial allergy. VII. Bronchial desensitization and resensitization in passively sensitized guinea pigs, 157
—, WESTERVELT, F. B., JR., AND TULL, LOUISE N. Prevention of bronchial reactions to aerosols of specific haptens by pretreatment with aerosols of Pyribenzamine and Isuprel, 153

T

TERPLAN, KORNEL L. (*See* ARBESMAN, TERPLAN, NETER, AND BERTRAM), 123
TOTTEN, ROBERT S. (*See* CRIEP, SCHEPARTZ, LEVINE, AND TOTTEN), 519
TUFT, LOUIS. (*See* ETTELSON AND TUFT), 88
— AND GREGORY, DONALD. Evaluation of the skin-testing methods employed in the diagnosis of penicillin allergy, 92 (Abst.)
— AND HECK, V. MURIEL. Studies in sensitization as applied to skin testing procedures. II. Influence of allergen contact, 59
—, GREGORY, JOAN, AND GREGORY, DONALD. Study of the effect of pantothenic acid upon allergic reactions, 92 (Abst.)
—, HECK, V. MURIEL, AND GREGORY, DONALD C. Studies in sensitization as applied to skin test reactions. III. Influence of age upon skin reactivity, 359
TULL, LOUISE. (*See* SILVETTE, SWINEFORD, AND TULL), 509

—. (*See* SWINEFORD AND TULL), 83
—. (*See* SWINEFORD, TULL, AND WESTERVELT), 157
—. (*See* SWINEFORD, WESTERVELT, AND TULL), 153

U

UNGER, LEON, AND SANTOS, I. N. Nasal polyps as related to allergic rhinitis and bronchial asthma, 92 (Abst.)

V

VENNING, E. H. (*See* ROSE, FYLES, AND VENNING), 1

W

WALZER, MATTHEW. A nine-year study of the effectiveness of New York City's ragweed extermination campaign, 84 (Abst.)

WANG, DAVID M. K. (*See* BURRAGE, WANG, AND IRWIN), 79
—, BURRAGE, WALTER S., IRWIN, JOHN W., AND ARONOW, SAUL (WITH THE TECHNICAL ASSISTANCE OF GORDON, PRISCILLA, AND GILCHRIST, MARY). Cortisone or hydrocortisone in the treatment of severe, intractable asthma? 448
WARREN, S. A. (*See* BENAIM, FEINBERG, WARREN, AND STERNBERGER), 86
—. (*See* STERNBERGER, FEINBERG, FEINBERG, BENAIM, AND WARREN), 82
WEISS, HARRY A. (*See* KEENEY, WEISS, AND MOHR), 141
WEISSMAN, LESTER. (*See* SIEGEL, COLEMAN, WEISSMAN, AND SHER), 78
WESTERVELT, F. B., JR. (*See* SWINEFORD, TULL, AND WESTERVELT), 157
—. (*See* SWINEFORD, WESTERVELT, AND TULL), 153

SUBJECT INDEX*

A

Abattoir workers, Brucella infection in, comparison between skin sensitivity and modified antiglobulin test in, *57* (Abst.)

Abortion, habitual, blood groups in, study of, *31* (Abst.)

Acacia as immunizing, sensitizing, anaphylactogenic, and desensitizing antigen, observations on (Silvette et al.), 509

ACTH and cortical steroids, simultaneous administration of, effect on adrenal weight and cholesterol concentration, *63* (Abst.)

and cortisone during rapid desensitization of allergic patients (Keeney et al.), 141

effect of, on passively transferred delayed hypersensitivity to 2,4-dinitrochlorobenzene in guinea pigs, *13* (Abst.)

on pathology of reversed anaphylaxis in guinea pig (Arbesman et al.), 123

in pregnancy, *16* (Abst.)

in treatment of asthma (Baldwin et al.), 44

of ulcerative colitis, *30* (Abst.)

use and abuse of, in allergic conditions, *81* (Abst.)

intravenous administration, changes in plasma levels of 17-hydroxycorticosteroids during. I. Test of adrenocortical capacity in human, *45* (Abst.)

prolonged treatment in rabbits, changes in patterns of secretion of corticosteroids after, *11* (Abst.)

release in rats, mechanism by which histamine stimulates, *46* (Abst.)

Adenitis, immunization, *91* (Abst.)

Adrenalectomy in guinea pig, effect of, on asthma from antigen aerosol and on its inhibition by nonspecific procedures (Benaim et al.) (Abst.), 86

Adrenocortical capacity in human, test of, *45* (Abst.)

psychiatric, and pulmonary observations in bronchial asthma (Knapp and Michelson) (Abst.), 80

Aeroallergen studies with molecular filter membrane (Gurney and Cryst), 533

Aeroallergens in Seattle (Frayser) (Abst.), 88

studies on (Gurney and Cryst) (Abst.), 84

Aerosol of compound 48/80, effect of, on reactivity to aerosol and intraperitoneal injections of (Feinberg and Sternberger), 176

therapy, formulary of (Rocchietta), 384 (B. rev.)

Aerosols of antigens, reactions to specific, prevention or amelioration of, by pretreatment with aerosols of antihistamines and sympathomimetics (Swineford and Motley) (Abst.), 91

of epoxytropine tropate methylbromide for relief of bronchospasm, *50* (Abst.)

of pollen extracts, treatment of pollen hay fever and asthma with (Swineford and Lucas) (Abst., 91); 305

of specific haptens, bronchial reactions to, prevention of, by pretreatment with aerosols of Pyribenzamine and Isuprel (Swineford et al.), 153

Age, influence of, upon skin reactivity (Tuft et al.), 359

Agglutination, demonstration of, by lymphocytes, *12* (Abst.)

Agranulocytosis following treatment with phenylindanedione, *54* (Abst.)

Air-borne, culturable fungus spores, numbers and kinds of, in Havana, Cuba (Alvarez and Castro), 150

spores, fungus colony counts from, in Birmingham, Alabama (Cason), 367

Alkali, recovery of normal and eczematous skin from, *67* (Abst.)

Allergen contact, influence of, in skin testing procedures in studies in sensitization (Tuft and Heck), 59

Allergenic extracts, highly concentrated, preparation of, by increasing concentration of extraction. I. Timothy and low ragweed pollens (Hampton et al.), 16

intravenous injection of, in hay fever and asthma, observations on (Lowell et al.) (Abst.), 86

factor, molds as, in New York metropolitan area (Merksamer and Sherman) (Abst.), 81

*Abstracts of papers presented at the American Academy of Allergy meeting are marked (Abst.) preceding the page number. *Allergy Abstracts*, indexed separately at the end of the JOURNAL, are marked (Abst.) following the italic page number.

Allergenicity of modified and processed foodstuffs. VII. Gelatin: anaphylactogenic properties of gelatin and its precursors (Ratner and Crawford) (Abst.), 91
Allergens in vegetable oils (Essellier et al.), 107
inhalant, in dermatitis, *85* (Abst.)
Allergic and pyrogenic transfusion reactions, antihistaminics for, *91* (Abst.)
blood donors, acceptability of, in American Red Cross Blood program, report of committee of American Academy of Allergy on, 181
conditions, ACTH and cortisone in, use and abuse of, *81* (Abst.)
treatment of, with sustained release chlorprophenpyridamine maleate, *16* (Abst.)
conjunctivitis, Cortogen and Chlor-Trimeton in treatment of, *39* (Abst.)
constitution, poliomyelitis and, *92* (Abst.)
contact dermatitis due to histamine-releasing drug 48-80, *83* (Abst.)
cutaneous vasculitis, *5* (Abst.)
dermatoses, histopathology of, *21* (Abst.)
desensitization, antihistamines by injection in, *66* (Abst.)
disorders, Meticorten and 9 alpha fluorohydrocortisone in treatment of (Arbesman and Ehrenreich), 189
eczematous contact-type dermatitis due to zoris, *37* (Abst.)
manifestations, Sandostene for treatment of, *75* (Abst.)
patients, desensitization of, use of cortisone or ACTH during (Keeney et al.), 141
reaction to PAS, fatal, *54* (Abst.)
reactions, delayed, study of blocking effect of plasma and lysed red blood cells on, *14* (Abst.)
effect of pantothenic acid upon (Tuft et al.) (Abst.), 92
to bee and wasp stings, *24* (Abst.)
rhinitis and bronchial asthma, nasal polyps as related to (Unger and Santos) (Abst.), 92
cerebrospinal rhinorrhea simulating (Berryman), 71
intranasal corticotrophin in, *38* (Abst.)
nasal hydrocortisone in (Ogden et al.) (Abst.), 78
of pollen origin, treatment of, by use of suspension of Cortogen acetate with Chlor-Trimeton maleate, *34* (Abst.)
Allergies, miscellaneous, *7, 23, 39, 53, 72, 86* (Absts.)
nasal, Prantal orally in treatment of, *2* (Abst.)
respiratory, childhood complications of (Howard) (Abst.), 88
Allergist and preventive medicine, 75 (Editorial)
Allergology, second International Congress of, 187 (Announcement); 180 (Editorial)
Allergy, dilemma in (Prince), 279
and hypersensitivity, blood in, role of formed elements of (symposium: Chase et al.), 219
bacterial, sinus disease, and bronchial asthma (Siegal et al.) (Abst.), 80
studies in. VII. Bronchial desensitization and resensitization in passively sensitized guinea pigs (Swineford et al.), 157
clinical studies in, with several new drugs (Arbesman) (Abst.), 87
defective hearing due to, antihistamine in, *38* (Abst.)
drug, swelling of interphalangeal joints as manifestation of, *74* (Abst.)
Foundation of Northern California, 555 (Announcement)
in ophthalmology, common manifestations of, *39* (Abst.)
inhalant, summer blooming lamb's-quarters a factor in, *83* (Abst.)
intravenous hydrocortisone in, *82* (Abst.)
penicillin, skin-testing methods in diagnosis of, evaluation of (Tuft and Gregory) (Abst.), 92
platelet antibodies in (Dameshek), 229
practice of (Vaughan), 94 (B. rev.)
reagins, relation of, to electrophoretic components of serum, *15* (Abst.)
red blood cells in (Haberman), 219
regional, of United States, Canada, Mexico, and Cuba (symposium edited by Samter and Durham), 383 (B. rev.)
residencies in, 93, 556 (Announcements)
to citric acid (Ettelson and Tuft) (Abst.), 88
undergraduate medical education in (Sheldon), 275
Alternaria, fibrocrystalloid antigen from (Sternberger et al.) (Abst.), 82
Alveolar-arterial oxygen tension gradient in chronic pulmonary disease, evaluation of factors affecting, *64* (Abst.)
American Academy of Allergy, historian's report, Feb. 7, 1955 (Howes), 283
1956 annual meeting program, 553
postgraduate teaching program, 77
president's address (Sheldon), 275
report of committee on acceptability of allergic donors in American Red Cross Blood program, 181
report of committee on drugs of Research Council, 1954-1955, 377
report of Research Council (Samter), 474
Aminophylline, Dapanone, and Isuprel, effects of, in bronchial asthma; method for objective evaluation of bronchodilator drugs (Cander and Comroe), 210

Aminophylline—Cont'd
effect on cerebral hemodynamics in presence of cardiac failure with and without Cheyne-Stokes respiration, *28* (Abst.)
Ammodytes viper venom, antigenic composition of, *16* (Abst.)
Anaphylactic reaction caused by mixture of penicillin-streptomycin-procaine, *55* (Abst.)
severe, from oral penicillin, *25* (Abst.)
shock following cobalt-60 gamma radiation, susceptibility of mice to, *8* (Abst.)
production of lipemia-clearing factor during, *10* (Abst.)
Anaphylactogenic antigen, acacia as (Silvette et al.), 509
properties of gelatin and its precursors (Ratner and Crawford), 320
of piperazine citrate, *72* (Abst.)
Anaphylactoid inflammatory responses to preparations of duodenal intrinsic factors and gastric mucin, *30* (Abst.)
Anaphylaxis, *8*, *25*, *44*, *74* (Absts.)
histamine in (Dragstedt), 287
passive, in dog, quantitative study, *25* (Abst.)
in pertussis-vaccinated mice, quantitative aspects of, *44* (Abst.)
reversed, in guinea pig, effects of ACTH and cortisone on pathology of (Arbesman et al.), 123
Anergy, cutaneous, and Hodgkin's disease, *22* (Abst.)
Angioedema and urticaria in children and young adults, *5* (Abst.)
Animal tissues, quantitative determination of histamine in (McIntire), 292
Announcements, 93, 187, 286, 382, 479, 555
Antepar, anaphylactogenic properties of, *72* (Abst.)
Antibiotic therapy, fatal Shwartzman reaction during, *31* (Abst.)
Antibodies in skin of guinea pig, effect of histamine upon local fixation of, *25* (Abst.)
platelet, in allergy (Dameshek), 229
Antibody formation and effect of x-irradiation on circulating antibody levels in hypophysectomized rat, *13* (Abst.)
in mature rabbits, inhibition of, by contact with antigen at early age, *9* (Abst.)
in x-irradiated rabbits, quantitative serological determinations of, *13* (Abst.)
in anti-egg albumin sera, unidentified, revealed by agar diffusion technic, *10* (Abst.)
production, local, studies on, *12* (Abst.)
skin-sensitizing, electrophoretic separation of, from sera of ragweed-sensitive patients (Rose et al.) (Abst.), 86; (Sehon et al.), 329
Anticholinergic agent, new, piperphenamine, for control of hyperhidrosis and associated dermatoses, *4* (Abst.)
Anti-egg albumin sera, unidentified antibody in, revealed by agar diffusion technic, *10* (Abst.)
Antigen aerosol, asthma from, in guinea pig, effect of adrenalectomy on (Benaim et al.) (Abst.), 86
effect of intraperitoneal injections of compound 48/80 on response to (Feinberg and Sternberger), 176
dosage, massive, effect of, on antigen retention and antibody response in rabbits, *88* (Abst.)
fibrocrystalloid, from alternaria (Sternberger et al.) (Abst.), 82
house dust, source of, studies on (Follensby et al.) (Abst.), 80
immunizing, sensitizing, anaphylactogenic, and desensitizing, acacia as (Silvette et al.), 509
Antigens, aerosols of, reactions to specific, prevention or amelioration of, by pretreatment with aerosols of antihistamines and sympathomimetics (Swineford and Motley) (Abst.), 91
erythrocyte, human (Haberman), 220
multiple, blood histamine release and skin test response to, correlation of (Noah and Brand) (Abst., 84); 385
ragweed, identification of, in gel diffusion precipitates, *49* (Abst.)
Antihistamine, new, for treatment of allergic manifestations, *75* (Abst.)
buclizine hydrochloride (Vibazine), clinical evaluation of (Gaillard), 373
effect of, on compound 48/80 reaction (Feinberg and Sternberger), 177
in defective hearing due to allergy, *38* (Abst.)
Vibazine, clinical evaluation of (Gaillard), 373
Antihistamines by injection in allergic desensitization, *66* (Abst.)
parenteral and oral, in preventing penicillin reactions (Mathews et al.) (Abst.), 78
Antihistaminic compounds containing pyridine radical, quantitative method for determination of, *75* (Abst.)
drug, Diphenylpyraline, report of committee on drugs of Research Council of American Academy of Allergy, 1954-1955, 377
drugs, effect of, on mammalian capillary bed, *62* (Abst.)
in treatment of nonhemolytic transfusion reactions, *91* (Abst.)
for allergic and pyrogenic transfusion reactions, *91* (Abst.)
Antihistaminics, inefficacy of, upon secretion of gastric juices, interpretation of (Stern), 268

Aqua Ivy; treatment of sensitive patients and toxicity studies on guinea pig (Passenger et al.) (Abst.), 90
Arsenic in treatment of asthma, *51* (Abst.)
Arteriolitis allergica, *5* (Abst.)
Arthritis, phenylbutazone treatment for, erythema multiforme bullosum following, *52* (Abst.)
Arthus desensitization (Swineford and Tull) (Abst.), 83
Asthma, ACTH and cortisone in treatment of (Baldwin et al.), 44
and hay fever, *2*, *17*, *33*, *49*, *65*, *81* (Absts.)
aerosols of pollen extracts in treatment of (Swineford and Lucas) (Abst.), 91
intravenous injection of allergenic extracts in, observations on (Lowell et al.) (Abst.), 86
pollen, treatment of, with aerosols of pollen extracts (Swineford et al.), 305
summer, prophylaxis of, *18* (Abst.)
arsenic in treatment of, *51* (Abst.)
bronchial, cortisone treatment of, two deaths during, *51* (Abst.)
C-reactive protein levels and anti-streptolysin O titres in, *52* (Abst.)
Demerol in, *17* (Abst.)
effects of Dapanone, Isuprel, and aminophylline in (Cander and Comroe), 210
metacortandracin in (Schwartz), 206
nasal polyps as related to (Unger and Santos) (Abst.), 92
pathology of. I. Significance of membrane changes in asthmatic and non-allergic pulmonary disease (Crepea and Harman), 453
positive skin reactions unrelated to, psychosomatic study of (Miller and Baruch), 54
prednisone in (Schwartz), 206
psychiatric, pulmonary, and adrenocortical observations in (Knapp and Michelson) (Abst.), 80
psychosomatic study of unrelated positive skin reactions (Miller and Baruch), 54
respiratory function in, effect of corticotropin and cortisone on (Fyles et al.), 340
severe intractable, cortisone or hydrocortisone in treatment of (Burrage et al.) (Abst.), 79
severity of, estimation of daily changes in (Lowell et al.), 113
sinus disease, bacterial allergy, and (Siegal et al.) (Abst.), 80
with diabetes mellitus, comparative effects of metacortandracin, hydrocortisone, and cortisone in (Schwartz), 206
with nasal polyps, comparative effects of metacortandracin, hydrocortisone, and cortisone in (Schwartz), 206
Asthma—Cont'd
chronic, metacortandracin in (Skaggs et al.), 201
compound F, oral use of, in, *33* (Abst.)
corticoid excretion in, effect of bed rest on (Rose et al.), 2
death in, unexpected, *66* (Abst.)
from antigen aersols in guinea pig, effect of adrenalectomy on (Benaim et al.) (Abst.), 86
in relation to hyperglycemia and diabetes mellitus, corticotrophin, cortisone, and hydrocortone therapy in (Rose) (Abst.), 79
membrane changes in, significance of (Crepea and Harman), 453
Prantal, orally, in treatment of, *2* (Abst.)
severe, intractable, cortisone or hydrocortisone in treatment of (Wang et al.), 448
smoker's, observations on, *3* (Abst.)
spontaneous pneumothorax complicating (Crepea) (Abst.), 88
urinary corticoid excretion during attacks of (Rose et al.), 4
vital capacity of, and forced respiratory curves in (Roy et al.), 490
Asthmagram, cases illustrating its use (Swineford et al.) (Abst.), 91
Asthmatic child, gamma-globulin and (Bowen) (Abst.), 87
patients, pulmonary function in, effect of helium-oxygen mixtures on (Schiller et al.), 11
sputum, chemical nature of, preliminary observations on (Bukantz and Schiele) (Abst.), 85
Atmosphere, fungi encountered in, studies on, *66*, *68* (Absts.)
Atmospheric mold counts in Toronto, Canada (Collins-Williams and Best), 488
pollen counts in Toronto, Canada (Collins-Williams and Best), 461
Atopic dermatitis, histologic and histochemical changes in (Rappaport) (Abst.), 82
Study of natural course and of wool as dominant allergenic factor, *35* (Abst.)
urinary corticoid excretion in urticaria and (Rose et al.), 6
eczema, personality factors in adult, *36* (Abst.)
Autoimmunologic disease (Cavelti), 95
Award to Dr. Bret Ratner, 555 (Announcement)

B

Bacterial allergy, sinus disease, and bronchial asthma (Siegal et al.) (Abst.), 80
studies in. VII. Bronchial desensitization and resensitization in passively sensitized guinea pigs (Swineford et al.), 157
BCG infection in guinea pig, effect of cortisone on, *42* (Abst.)

Bed rest, effect of, on corticoid excretion in asthma (Rose et al.), 2
Bedbug bite anaphylaxis misinterpreted as coronary occlusion, *92* (Abst.)
Bee and wasp stings, allergic reactions to, *24* (Abst.)
Benzathine penicillin, intramuscular, prolonged reaction to, *58* (Abst.)
Betaprone, human reagins exposed to, activity of (Flick and Feinberg), 262
Beta-propiolactone, disinfectant, activity of human reagins exposed to (Flick and Feinberg), 262
Biological corticoid excretion during acute symptoms in diseases of hypersensitivity (Rose et al.), 1
Blood and lymph node studies of severe paraaminosalicylic acid hypersensitivity, *87* (Abst.)
  autoimmune diseases of (Cavelti), 99
  cell count response to epinephrine in splenectomized dogs, *47* (Abst.)
  donors, allergic, acceptability of, in American Red Cross program, report of committee of American Academy of Allergy on, 181
  eosinophils of, during prolonged exposure to cold and chronic administration of cortisone acetate, *15* (Abst.)
  groups in habitual abortion, study of, *31* (Abst.)
  histamine release and skin test response to multiple antigens, correlation of (Noah and Brand) (Abst., 84); 385
  in allergy and hypersensitivity, formed elements of (symposium: Chase et al.), 219
  thyroid hormone level in, effect of epinephrine on, *11* (Abst.)
  volume in patients in status asthmaticus and during normal period (Lovell et al.) (Abst.), 90
Book reviews, 94, 383
Brazilian currency exchange, 479 (Announcement)
Bronchial asthma, cortisone treatment of, two deaths during, *51* (Abst.)
  C-reactive protein levels and anti-streptolysin O titres in, *52* (Abst.)
  Demerol in, *17* (Abst.)
  effects of Dapanone, Isuprel, and aminophylline in (Cander and Comroe), 210
  metacortandracin in (Schwartz), 206
  nasal polyps as related to (Unger and Santos) (Abst.), 92
  pathology of. I. Significance of membrane changes in asthmatic and non-allergic pulmonary disease (Crepea and Harman), 453
  positive skin reactions unrelated to, psychosomatic study of (Miller and Baruch), 54
  prednisone in (Schwartz), 206
Bronchial asthma—Cont'd
  psychiatric, pulmonary, and adrenocortical observations in (Knapp and Michelson) (Abst.), 80
  respiratory function in, effect of corticotropin and cortisone on (Fyles et al.), 340
  severe intractable, cortisone or hydrocortisone in treatment of (Burrage et al.) (Abst.), 79
  severity of, estimation of daily changes in (Lowell et al.), 113
  sinus disease, and bacterial allergy (Siegal et al.) (Abst.), 80
  with diabetes mellitus, comparative effects of metacortandracin, hydrocortisone, and cortisone in (Schwartz), 206
  with nasal polyps, comparative effects of metacortandracin, hydrocortisone, and cortisone in (Schwartz), 206
  desensitization and resensitization in passively sensitized guinea pigs: studies in bacterial allergy (Swineford et al.), 157
  reactions to aerosols of specific haptens, prevention of, by pretreatment with aerosols of Pyribenzamine and Isuprel (Swineford et al.), 153
  tree, thickened basement membrane in, significance of (Crepea) (Abst.), 80
Bronchodilator drugs, objective evaluation of, method for (Cander and Comroe), 210
Bronchospasm, Pamine for relief of, *50* (Abst.)
Bronchospirometry, effect on respiration of occlusion of bronchus in man during, *46* (Abst.)
Brucella infection in abattoir workers, comparison between cutaneous sensitivity test and modified antiglobulin test in, *57* (Abst.)
Brucellosis, human, standardized antigen and agglutination technic for, *30* (Abst.)
Buclizine hydrochloride, new antihistamine, clinical evaluation of (Gaillard), 373
Butyric acid, reaction to (Essellier et al.), 108

C

Caffeine alkaloid, ergotamine tartrate and, rectal use of, for relief of migraine, *8* (Abst.)
Canada fleabane for soybean diarrhea (Blue), 425
Canadian Academy of Allergy, 93, 188 (Announcement)
Capillaries, effect of roentgen irradiation on, *90* (Abst.)
Capillary bed, mammalian, effect of antihistaminic drugs on, *62* (Abst.)

Cement, chromium content of, and its significance in cement dermatitis, *7* (Abst.)
Cerebrospinal rhinorrhea simulating allergic rhinitis (Berryman), 71
Cheilitis due to coffee, *20* (Abst.)
Chemical investigation of ragweed pollen extracts (Frankel et al.), 33
nature of asthmatic sputum, preliminary observations on (Bukantz and Schiele) (Abst.), 85
Children, penicillin reactions in (Matheson and Elegant), 415
skin test in penicillin sensitization in (Matheson and Elegant), 415
Chlorprophenpyridamine maleate, sustained release, treatment of allergic conditions with, *16* (Abst.)
Chlor-Trimeton and Cortogen in treatment of allergic conjunctivitis, *39* (Abst.)
Citric acid, allergy to (Ettelson and Tuft) (Abst.), 88
Citrus flavinoids in respiratory infections, *30* (Abst.)
Coal tar, eczematous hypersensitivity to, *21* (Abst.)
Cobalt-60 gamma radiation, anaphylactic shock following, susceptibility of mice to, *8* (Abst.)
Coffee, cheilitis due to, *20* (Abst.)
Colitis, ulcerative, ACTH and cortisone in treatment of, *30* (Abst.)
Collegium Internationale Allergologicum, 479 (Announcement)
Compound F, oral, in asthma, *33* (Abst.)
Compound 48/80 histamine liberator, action of, in guinea pig (Feinberg and Sternberger), 170
Conjunctivitis, allergic, Cortogen and Chlor-Trimeton in treatment of, *39* (Abst.)
Contact dermatitis, allergic, due to histamine-releasing drug 48-80, *83* (Abst.)
dinitrochlorobenzene, in guinea pigs, *4* (Abst.)
effects of x-rays on experimentally produced, *69* (Abst.)
from chloreyclizine hydrochloride (Perazil) cream, *68* (Abst.)
from platinum and related metals, *83* (Abst.)
Coronary occlusion, bedbug bite anaphylaxis misinterpreted as, *92* (Abst.)
Cortical steroids and ACTH, simultaneous administration of: effect on adrenal weight and cholesterol concentration, *63* (Abst.)
Corticoid therapy of atopic dermatitis, histologic and chemical changes following (Rappaport) (Abst.), 82
Corticosteroids, changes in patterns of secretion of, in rabbits after prolonged treatment with ACTH, *11* (Abst.)
Corticotropin and cortisone, effect of, on respiratory function in bronchial asthma (Fyles et al.), 340
cortisone, and hydrocortisone in diseases of hypersensitivity. I. Biological corticoid excretion during acute symptoms (Rose et al.), 1
and hydrocortone therapy in asthma in relation to hyperglycemia and diabetes mellitus (Rose) (Abst.), 79
death from, *41* (Abst.)
intranasal, in hay fever and allergic rhinitis, *38* (Abst.)
Cortisone and ACTH during rapid desensitization of allergic patients (Keeney et al.), 141
effect of, on passively transferred delayed hypersensitivity to 2, 4-dinitrochlorobenzene in guinea pigs, *13* (Abst.)
on pathology of reversed anaphylaxis in guinea pig (Arbesman et al.), 123
in pregnancy, *16* (Abst.)
in treatment of asthma (Baldwin et al.), 44
of ulcerative colitis, *30* (Abst.)
use and abuse of, in allergic conditions, *81* (Abst.)
and corticotropin, effect of, on respiratory function in bronchial asthma (Fyles et al.), 340
antagonism of, to body temperature-reducing effect of histamine, *10* (Abst.)
corticotrophin, and hydrocortisone in diseases of hypersensitivity. I. Biological corticoid excretion during acute symptoms (Rose et al.), 1
and hydrocortone therapy in asthma in relation to hyperglycemia and diabetes mellitus (Rose) (Abst.), 79
during penicillin treatment of secondary mucocutaneous syphilis in hypersensitive patient, *20* (Abst.)
effect of, on BCG infection in guinea pig, *42* (Abst.)
on plasma globulins in dogs, *90* (Abst.)
volume changes in egg white-injected rats, *12* (Abst.)
on vascular reactivity, *63* (Abst.)
inhibition by, of binding of new histamine in rat tissues, *46* (Abst.)
metacortandracin, and hydrocortisone, comparative effects of, in bronchial asthma with diabetes mellitus and bronchial asthma with nasal polyps (Schwartz), 206
ointment in treatment of eczema, *34* (Abst.)
or hydrocortisone in treatment of severe intractable bronchial asthma (Burrage et al.) (Abst.), 79; (Wang et al.), 448

Cortisone and ACTH—Cont'd
sensitivity of circulating eosinophils and capillary resistance to, *90* (Abst.)
therapy of serum neuritis, dramatic response to, *86* (Abst.)
thromboembolic complications from, risk of, *29* (Abst.)
treatment of bronchial asthma, two deaths during, *51* (Abst.)
Cortogen and Chlor-Trimeton maleate in treatment of allergic conjunctivitis, *39* (Abst.)
of allergic rhinitis of pollen origin, *34* (Abst.)
Crabs, porcelain, pruritus produced by zooea larvae of one of, *22* (Abst.)
Culturable fungus spores, air-borne, numbers and kinds of, in Havana, Cuba, (Alvarez and Castro), 150
Cutaneous anergy and Hodgkin's disease, *22* (Abst.)
Cytology of tuberculin reaction in skin windows in man, *40* (Abst.)

D

Dapanone, Isuprel, and aminophylline, effects of, in bronchial asthma (Cander and Comroe), 210
Demerol in bronchial asthma, *17* (Abst.)
Dermal sensitization, duration of, following cellular transfer in guinea pigs (Chase and Ballisto) (Abst.), 83
Dermatitis, allergic contact, due to histamine-releasing drug 48-80, *83* (Abst.)
eczematous contact-type due to zoris, *37* (Abst.)
atopic, histologic and histochemical changes in (Rappaport) (Abst.), 82
study of its natural course and of wool as dominant allergenic factor, *35* (Abst.)
urinary corticoid excretion in (Rose et al.), 6
cement, chromium content of cement and its significance in, *7* (Abst.)
contact, dinitrochlorobenzene, in guinea pigs, *4* (Abst.)
effect of x-rays on experimentally produced, *69* (Abst.)
from chlorcyclizine hydrochloride cream, *68* (Abst.)
from Perazil cream, *68* (Abst.)
from platinum and related metals, *85* (Abst.)
from waterless hand cleaners, *21* (Abst.)
hand, etiologic appraisal of, *84, 85* (Absts.)
inhalant allergens in, *85* (Abst.)
soap and detergents as primary irritants in, *85* (Abst.)
hydrocortisone acetate ointment in, *3* (Abst.)
Dermatitis—Cont'd
in guinea pigs produced by crude ether-soluble extracts of alternaria, hormodendrum, penicillium, and Aspergillus, *66* (Abst.)
inhalant allergens in, *85* (Abst.)
occupational, in government workers, *4* (Abst.)
of feet due to shoes, *69* (Abst.)
Rhus, treatment of, with topical hydrocortisone, *67* (Abst.)
venenata from tree pollen oils (Lovell et al.) (Abst., 89); 408
Dermatology, *3, 20, 34, 52, 66, 83* (Absts.)
hydrocortisone ointments in, *6* (Abst.)
Dermatoses, allergic, histopathology of, *21* (Abst.)
fluorhydrocortisone acetate topically applied in, *70* (Abst.)
prednisone in treatment of, *70* (Abst.)
Dermographism, low incidence of, in subacute and chronic urticaria, *36* (Abst.)
Desensitization, allergic, antihistamines by injection in, *66* (Abst.)
and resensitization, bronchial, in passively sensitized guinea pigs (Swineford et al.), 157
arthus (Swineford and Tull) (Abst.), 83
of penicillin-sensitive patients, *23* (Abst.)
rapid, of allergic patients, use of cortisone or ACTH during (Keeney et al.), 141
Desensitizing antigen, acacia as (Silvette et al.), 509
Detergents and soaps as primary irritants in hand dermatitis, *85* (Abst.)
as sensitizers in hand dermatitis, *84* (Abst.)
Diabetes, insulin-resistant, after total pancreatectomy, *42* (Abst.)
mellitus and hyperglycemia, asthma in relation to, corticotrophin, cortisone, and hydrocortone therapy in (Rose) (Abst.), 79
bronchial asthma with, comparative effects of metacortandracin, hydrocortisone, and cortisone in (Schwartz), 206
Diarrhea, infantile, Shwartzman phenomenon in fatal, *78* (Abst.)
soybean, folklore remedy for (Blue), 425
Dibucaine hydrochloride lozenges, fatal poisoning from, *86* (Abst.)
Dicumarol, effect on localized Shwartzman reaction, *20* (Abst.)
Diethyl-aminoethyl theophylline hydrochloride, cerebral hemodynamic response to, *29* (Abst.)
Dilemma in allergy (Prince), 279
Dinitrochlorobenzene contact dermatitis in guinea pigs, *4* (Abst.)
Diphenylpyraline, antihistaminic drug, report of committee of Research Council of American Academy of Allergy on, 377

Diphtheria antitoxin, studies of, in rheumatic fever subjects, *47* (Abst.)
Disinfectant, beta-propiolactone, activity of human reagins exposed to (Flick and Feinberg), 262
Drug allergy, swelling of interphalangeal joints as manifestation of, *74* (Abst.)
eruption from sulfonamides, *86* (Abst.)
therapy, reactions with (Alexander), 383 (B. rev.)
Drugs, antihistaminic, effect of, on mammalian capillary bed, *62* (Abst.)
Bronchodilator, objective evaluation of, method for (Cander and Comroe), 210
new, clinical studies in allergy with several (Arbesman) (Abst.), 87
evaluation of, 273 (Editorial)
report of committee on, of Research Council of American Academy of Allergy, 1954-1955, 377
sensitizing properties of, experimental methods for detection of, shortcomings of (Mayer), 133
Dust, house, analysis and standardization of, by gel diffusion, *7* (Abst.)
antigen, source of, studies on (Follensby et al.) (Abst.), 80

E

Eczema, atopic, personality factors in adult, *36* (Abst.)
nummular, etiology of, *6* (Abst.)
treatment of, with cortisone ointment, *34* (Abst.)
Eczematous hypersensitivity to coal tar, *21* (Abst.)
Editorial, evaluation of new drugs, 273
second International Congress on Allergology, 180
the allergist and preventive medicine, 75
Electrophoretic separation of skin-sensitizing antibody from sera of ragweed-sensitive patients (Sehon et al.), 329
Eosinophilic granuloma of lungs, *15* (Abst.)
Eosinophils in allergy and hypersensitivity (Samter), 248
of blood during prolonged exposure to cold and chronic administration of cortisone acetate, *15* (Abst.)
Epinephrine, blood cell count response to, in splenectomized dogs, *47* (Abst.)
effect of, on thyroid hormone level in blood, *11* (Abst.)
potentiation of effects of, by flavenoid compounds, *62* (Abst.)
Epoxytropine tropate methylbromide, aersols of, for relief of bronchospasm, *50* (Abst.)
Ergotamine tartrate and caffeine alkaloid, rectal use of, for relief of migraine, *8* (Abst.)
Erythema multiforme bullosum following phenylbutazone treatment for arthritis, *52* (Abst.)
Erythrocyte antigens, human (Haberman), 220
Esophagus, rupture of, complication of status asthmaticus, *51* (Abst.)
Experimental autoimmunologic diseases (Cavelti), 97
contact dermatitis. I. Dinitrochlorobenzene contact dermatitis in guinea pigs, *4* (Abst.)
glomerulonephritis produced by foreign protein, natural history of, *28* (Abst.)
hypersensitivity in rabbits, serum electrophoretic pattern in (Criep et al.) (Abst., 85); 519
methods for detection of sensitizing properties of new drugs, shortcomings of (Mayer), 133
production of arteritis by passive sensitization, effect of biologic and chemical agents on. II. Nitrogen mustard, *9* (Abst.)

F

Febrile syndrome during hydralazine treatment for hypertension, *24* (Abst.)
Feet, dermatitis of, due to shoes, *69* (Abst.)
Fibrocrystalloid antigen from alternaria (Sternberger et al.) (Abst.), 82
Filter, new micro Seitz type, (Strauss and Spain), 471
Flavenoid compounds, potentiation of effects of epinephrine by, *62* (Abst.)
Fluorhydrocortisone acetate, topically applied in dermatoses, *70* (Abst.)
and Meticorten in treatment of allergic disorders (Arbesman and Ehrenreich), 189
Folklore remedy for soybean diarrhea (Blue), 425
Food tests in allergies and controls; studies in sensitization as applied to skin testing procedures (Tuft and Heck), 67
Foodstuffs, allergenicity of modified and processed. VII. Gelatin: anaphylactogenic properties of gelatin and its precursors (Ratner and Crawford) (Abst.), 91
Fractionation of pollen extracts. II. Chemical and paper chromatographic investigation of ragweed pollen extracts (Frankel et al.), 33
of ragweed pollen extracts (Perlman) (Abst.), 86
Friedländer bacillus in chronic respiratory disease, role of, *19* (Abst.)
Fungi encountered in atmosphere, studies on. I. Presence of fungus spores and of pollens in KOH preparations, *68* (Abst.)
II. Production of dermatitis in guinea pigs by crude ether-soluble extracts of alternaria, hormodendrum, penicillium, and Aspergillus, *66* (Abst.)

Fungus colony counts from air-borne spores in Birmingham, Alabama (Cason), 367
spores, air-borne, culturable, numbers and kinds of, in Havana, Cuba (Alvarez and Chase), 150

G

Gamma-globulin and asthmatic child (Bowen) (Abst.), 87
Gastric juices, secretion of, inefficacy of antihistaminics upon (Stern), 268
Gel diffusion, analysis and standardization of house dust by, *7* (Abst.)
of proteins by, *73* (Abst.)
precipitates, identification of ragweed antigens in, *49* (Abst.)
Gelatin, anaphylactogenic properties of (Ratner and Crawford) (Abst.), 91
and its precursors, anaphylactogenic properties of (Ratner and Crawford), 320
Glomerulonephritis, autoantibodies to kidney in acute and chronic (Cavelti), 100
experimental, produced by foreign protein, natural history of, *28* (Abst.)
Glycerine in preparation and preservation of ragweed pollen extract, studies on optimum concentration of (Johnson et al.) (Abst., 89); 429
Grasses, pollen counts of, in Toronto, Canada (Collins-Williams and Best), 466
Guillain-Barrés syndrome, near-fatal shock from PAS followed by, *43* (Abst.)

H

Hand dermatitis, etiologic appraisal of, *84*, *85* (Absts.)
inhalant allergens in, *85* (Abst.)
soap and detergents as primary irritants in, *85* (Abst.)
Hay fever and asthma, *2*, *17*, *33*, *49*, *65*, *81* (Absts.)
aerosols of pollen extracts in treatment of (Swineford and Lucas) (Abst.), 91
intravenous injection of allergenic extracts in, observations on (Lowell et al.) (Abst.), 86
pollen, treatment of, with aerosols of pollen extracts (Swineford et al.), 305
summer, prophylaxis of, *18* (Abst.)
intranasal corticotrophin in, *38* (Abst.)
problem, meteorologic approach to (Dingle), 297
Hearing, defective, due to allergy, antihistamine in, *38* (Abst.)
Helium, open circuit, method for measuring functional residual capacity and defective intrapulmonary gas mixing, *19* (Abst.)
Helium-oxygen mixtures, effect of, on pulmonary function in asthmatic patients (Schiller et al.), 11
Hemolytic antibodies, production of, in rat, influence of somatotrophic hormone and hydrocortisone acetate on, *48* (Abst.)
effect of primaquine. II. Natural course of hemolytic anemia and mechanism of its self-limited character, *60* (Abst.)
III. Study of primaquine-sensitive erythrocytes, *61* (Abst.)
IV. Relation of cell age to hemolysis, *61* (Abst.)
Histamine, body temperature-reducing effect of, antagonism of cortisone to, *10* (Abst.)
effect of, upon local fixation of antibodies in skin of guinea pig, *25* (Abst.)
liberator compound 48/80, action of, in guinea pig (Feinberg and Sternberger), 170
effect of, in histamine-sensitive mice (Kind), 507
mechanism by which, stimulates ACTH release in rats, *46* (Abst.)
metabolism in diseases of liver, *28* (Abst.)
new, binding of, in rat tissues, inhibition by cortisone of, *46* (Abst.)
pharmacology of, and role in anaphylaxis (Dragstedt), 287
quantitative determination of, in animal tissues (McIntire), 292
release, blood, correlation of skin test response to multiple antigens and (Noah and Brand), 385
by mast cells, cytological and pharmacological observations on, *27* (Abst.)
skin test reactions to, in nonallergic persons (Tuft et al.), 363
toxicity of, and antagonism between histamine and antihistamines in various strains of mice, *74* (Abst.)
Histamine-liberators, effects of, on mast cells of rat, *45* (Abst.)
Histamine-releasing drug 48/80, allergic contact dermatitis due to, *83* (Abst.)
Histamine-sensitive mice, effect of histamine liberator 48/80 in (Kind), 507
Histopathology of allergic dermatoses, *21* (Abst.)
Historian's report, American Academy of Allergy, Feb. 7, 1955 (Howes), 283
Hodgkin's disease, cutaneous anergy and, *22* (Abst.)
Horse serum, skin reactions to; studies in sensitization as applied to skin testing procedures (Tuft and Heck), 62

House dust, analysis and standardization of, by gel diffusion, *7* (Abst.)
antigen, source of, studies on (Follensby et al.) (Abst.), 80
Hydralazine treatment for hypertension, prolonged, febrile syndrome during, *24* (Abst.)
Hydrocortisone acetate and somatotrophic hormone, influence of, on production of hemolytic antibodies in rat, *48* (Abst.)
local use of, in dermatology, *3* (Abst.)
ointment in skin diseases, *70* (Abst.)
corticotrophin, and cortisone in diseases of hypersensitivity. I. Biological corticoid excretion during acute symptoms (Rose et al.), 1
intravenous, clinical uses of, *59* (Abst.)
in allergy, *82* (Abst.)
metacortandracin, and cortisone, comparative effects of, in bronchial asthma with diabetes mellitus and bronchial asthma with nasal polyps (Schwartz), 206
nasal, in allergic rhinitis (Ogden et al.) (Abst.), 78
ointments, rational use in dermatology, *6* (Abst.)
or cortisone in treatment of severe, intractable bronchial asthma (Burrage et al.) (Abst.), 79; (Wang et al.), 448
topical, treatment of Rhus dermatitis with, *67* (Abst.)
Hydrocortone, corticotrophin, and cortisone therapy in asthma in relation to hyperglycemia and diabetes mellitus (Rose) (Abst.), 79
Hyperglycemia and diabetes mellitus, asthma in relation to, corticotrophin, cortisone, and hydrocortone therapy in (Rose) (Abst.), 79
Hyperhidrosis and associated dermatoses, piperphenamine, a new anticholinergic agent for control of, *4* (Abst.)
Hypersensitivity and allergy, role of formed elements of blood in (symposium: Chase et al.), 219
diseases of, corticotrophin, cortisone, and hydrocortisone in. I. Biological corticoid excretion during acute symptoms (Rose et al.), 1
eczematous, to coal tar, *21* (Abst.)
experimental, in rabbits, serum electrophoretic pattern in (Criep et al.) (Abst.), 85
serum electrophoretic pattern in (Criep et al.), 519
iodide, in etiology of periarteritis nodosa (Rasmussen), 394
lymphocytes in (Chase), 242
para-aminosalicylic acid, severe, *87* (Abst.)
penicillin, studies in. I. Immunologic findings in two penicillin sensitive patients (Siegel et al.) (Abst.), 78
Hypersensitivity and allergy—Cont'd
II. Significance of penicillin as contaminant (Coleman and Siegel), 253
"stresses" and (Benaim et al.), 481
to 2,4-dinitrochlorobenzene in guinea pigs, effect of cortisone and ACTH on, *13* (Abst.)
Hypertension, hydralazine treatment for, febrile syndrome during prolonged, *24* (Abst.)
Hyposensitization, oral, by oleoresin extracts, *36* (Abst.)

I

Illness in group of Cleveland families, study of. VI. Control studies of reactions to oxytetracycline hydrochloride, *23* (Abst.)
Immune response in rabbits, effect of polyvinylpyrrolidone infusions on. *89* (Abst.)
Immunity, antituberculous, induced in mice, *80* (Abst.)
Immunization adenitis, *91* (Abst.)
in rabbit, serum glycoprotein concentrations following, *89* (Abst.)
Immunizing antigen, acacia as (Silvette et al.), 509
Immunologic unresponsiveness induced by protein antigens, *77* (Abst.)
India ink, reticuloendothelial system of intravenously injected particles of, effect of hypophysectomy and various combinations of steroids and ACTH upon phagocytosis by, *61* (Abst.)
Infantile diarrhea, Shwartzman phenomenon in fatal, *78* (Abst.)
Infections, respiratory, citrus flavinoids in, *30* (Abst.)
Inhalant allergens in dermatitis, *85* (Abst.)
allergy, summer blooming lamb's-quarters factor in, *83* (Abst.)
Inhalational therapy with pressor drugs, safety of, *82* (Abst.)
Insulin, anaphylactic reaction from (Keeney et al.), 145
skin lesions from, nature and prevention of, *41* (Abst.)
Insulin-resistant diabetes after total pancreatectomy, *42* (Abst.)
International Congress of Allergology, second, 180 (Editorial); 187 (Announcement)
of Dermatology, eleventh, 555 (Announcement)
of Internal Medicine, fourth, 555 (Announcement)
Intranasal corticotrophin in hay fever and allergic rhinitis, *38* (Abst.)
Iodide hypersensitivity in etiology of periarteritis nodosa (Rasmussen), 394
sensitivity in etiology of periarteritis nodosa (Rasmussen) (Abst.), 81

Isoniazid and PAS, toxic reaction to, *53* (Abst.)
therapy, tuberculin reactions of tuberculous patients on, *56* (Abst.)
Isuprel and Pyribenzamine, pretreatment with aerosols of, to prevent bronchial reactions to aerosols of specific haptens (Swineford et al.), 153
Dapanone, and aminophylline, effects of, in bronchial asthma (Cander and Comroe), 210

J

Jewish National Home for Asthmatic Children, 286 (Announcement)

K

Kaposi's varicelliform eruption, direct transmission to nurse, *5* (Abst.)
KOH preparations, presence of fungus spores and of pollens in, *68* (Abst.)

L

Lamb's-quarters, summer blooming, factor in inhalant allergy, *83* (Abst.)
Leukocyte lysis, comparison of, with other immunologic phenomena in sera of tuberculous rabbits, *39* (Abst.)
Liver, diseases of, histamine metabolism in, *28* (Abst.)
Löffler's reaction to para-aminosalicylic acid, *73* (Abst.)
syndrome following use of vaginal cream, *24* (Abst.)
ocular manifestations in, *37* (Abst.)
Lung, functional residual capacity, open circuit helium method for measuring, and for defective intrapulmonary gas mixing, *19* (Abst.)
Lungs, eosinophilic granuloma of, *15* (Abst.)
Lupus erythematosus, systemic, hypothesis concerning pathogenesis of, *12* (Abst.)
Lymph node cells, studies on transfer of. III. Effects of variation in interval between injection of antigen into donor and collection of its lymph node cells, *26* (Abst.)
IV. Effect of x-irradiation of recipient rabbits on appearance of antibody after cell transfer, *14* (Abst.)
Lymphocytes, demonstration of agglutination by, *12* (Abst.)
in hypersensitivity (Chase), 242

M

Mast cells of rat, effects of histamine-liberators on, *45* (Abst.)
release of histamine by, cytological and pharmacological observations on, *27* (Abst.)
Medicine, preventive, allergist and, 75 (Editorial)
Ménière's disease, nonsurgical management of, *39* (Abst.)
Mercurial diuretics, reactions to, *74* (Abst.)
Metacortandracin, hydrocortisone, and cortisone, comparative effect of, in bronchial asthma with diabetes mellitus and bronchial asthma with nasal polyps (Schwartz), 206
in bronchial asthma (Schwartz), 206
in chronic asthma (Skaggs et al.), 201
in treatment of allergic disorders (Arbesman and Ehrenreich), 189
Meteorologic approach to hay fever program (Dingle), 297
Meticorten and 9 alpha fluorohydrocortisone in treatment of allergic disorders (Arbesman and Ehrenreich), 189
in chronic asthma (Skaggs et al.), 201
Metrorrhagia, uncommon symptom of constitutional reaction (Maietta) (Abst.), 90
Micro Seitz type filter, new (Strauss and Spain), 471
Migraine, rectal use of ergotamine tartrate and caffeine alkaloid for relief of, *8* (Abst.)
Mold counts, atmospheric, in Toronto, Canada (Collins-Williams and Best), 468
Molds, evaluation of, as allergenic factor in New York metropolitan area (Merksamer and Sherman) (Abst.). 81
isolated in air of Havana, Cuba (Alvarez and Castro), 151
Molecular filter membrane, aeroallergen studies with (Gurney and Cryst), 533
"Mule tail tea" for soybean diarrhea (Blue), 425

N

Nasal allergies, Prantal, oral, in treatment of, *2* (Abst.)
hydrocortisone in allergic rhinitis (Ogden et al.) (Abst.), 78
polyps as related to allergic rhinitis and bronchial asthma (Unger and Santos) (Abst.), 92
bronchial asthma with, comparative effects of metacortandracin, hydrocortisone, and cortisone in (Schwartz), 206
Nebulization therapy, improved method of, *18* (Abst.)
New York Medical College, postgraduate course in pediatric allergy, 382 (Announcement)
Nippostrongylus muris, absorption of protective antibodies from serum of, rats immune to, *31* (Abst.)
Nitrogen mustard, effect of, on experimental production of arteritis by passive sensitization, *9* (Abst.)
Nummular eczema, etiology of, *6* (Abst.)
Nuporal troches, fatal poisoning from, *86* (Abst.)

O

Occupational dermatitis in government workers, *4* (Abst.)
Ocular manifestations in Löffler's syndrome, *37* (Abst.)
Oils, tree pollen, dermatitis venenata from (Lovell et al.), 408
vegetable, allergens in (Essellier et al.), 107
Oleoresin extracts, oral hyposensitization by, *38* (Abst.)
Ophthalmology, allergy in, common manifestations of, *39* (Abst.)
Optimum concentration of glycerine in preparation and preservation of ragweed pollen extract, studies on (Johnson et al.), 429
Otorhinology and ophthalmology, *37*, *71* (Absts.)
Oudin's gel diffusion technique, analysis of proteins by, *73* (Abst.)
Oxygen and helium mixtures, effect of, on pulmonary function in asthmatic patients (Schiller et al.), 11
Oxytetracycline hydrochloride, reactions to, control studies of, *23* (Abst.)

P

Pamine for relief of bronchospasm, *50* (Abst.)
Pancreatectomy, total, insulin-resistant diabetes after, *42* (Abst.)
Pantothenic acid, effect of, upon allergic reactions (Tuft et al.) (Abst.), 92
Paper chromatographic investigation of ragweed pollen extracts (Frankel et al.), 33
Para-aminosalicylic acid, allergic reaction to, fatal, *54* (Abst.)
and Isoniazid, toxic reaction to, accompanied by leukopenia and atypical lymphocytosis, *53* (Abst.)
hypersensitivity, severe, *87* (Abst.)
Löffler's reaction to, *73* (Abst.)
Parephylin, xanthine compound, cerebral hemodynamic response to, *29* (Abst.)
PAS, allergic reaction to, fatal, *54* (Abst.)
and Isoniazid, toxic reaction to, *53* (Abst.)
hypersensitivity, severe; blood and lymph node studies, *87* (Abst.)
Löffler's reaction to, *73* (Abst.)
near-fatal shock from, followed by Guillain-Barrés syndrome, *43* (Abst.)
Passive anaphylaxis in dog, quantitative study of, *25* (Abst.)
in pertussis-vaccinated mice, quantitative aspects of, *44* (Abst.)
Pathology of bronchial asthma. I. Significance of membrane changes in asthmatic and nonallergic pulmonary disease (Crepea and Harman), 453
of reversed anaphylaxis in guinea pig, effects of ACTH and cortisone on (Arbesman et al.), 123
Penicillin allergy, skin-testing methods in diagnosis of, evaluation of (Tuft and Gregory) (Abst.), 92
as contaminant, significance of (Coleman and Siegel), 253
benzathine, intramuscular, prolonged reaction to, *58* (Abst.)
fatality following injection of, *43* (Abst.)
hypersensitivity, studies in. I. Immunologic findings in two penicillin sensitive patients (Siegel et al.) (Abst.), 78
II. Significance of penicillin as contaminant (Coleman and Siegel), 253
oral, severe anaphylactic reaction from, *25* (Abst.)
procaine, adverse reactions to, *57* (Abst.)
reactions in children (Matheson and Elegant), 415
prevention of, parenteral and oral antihistamines in (Mathews et al.) (Abst.), 78
procaine amide in treatment and prevention of, *72* (Abst.)
sensitive patient, desensitization of, *23* (Abst.)
sensitization, skin test in, value of (Matheson and Elegant), 415
S^{35}-labeled, autoradiographical distribution and excretion studies with, *11* (Abst.)
treatment of secondary mucocutaneous syphilis, in hypersensitive patient, use of cortisone during, *20* (Abst.)
Penicillin-streptomycin-procaine, anaphylactic reaction caused by mixture of, *55* (Abst.)
Perazil cream, contact dermatitis from, *68* (Abst.)
Periarteritis nodosa, iodide hypersensitivity in, etiology of (Rasmussen), 394
sensitivity in, etiology of (Rasmussen) (Abst.), 81
Pericarditis, acute, associated with serum sickness, *8* (Abst.)
Personality factors in adult atopic eczema, *36* (Abst.)
Pertussis-vaccinated mice, passive anaphylaxis in, quantitative aspects of, *44* (Abst.)
Pharmacology of histamine (Dragstedt), 287
physiology, and pathology, *10*, *26*, *45*, *59*, *74*, *88* (Absts.)
Phenylbutazone treatment for arthritis, erythema multiforme bullosum following, *52* (Abst.)
Phenylindanedione, agranulocytosis following treatment with, *54* (Abst.)
Piperazine citrate, anaphylactogenic properties of, *72* (Abst.)
Piperphenamine, new anticolinergic agent, for control of hyperhidrosis and associated dermatoses, *4* (Abst.)
Plasma and lysed red blood cells, blocking effect of, on delayed allergic reactions, *14* (Abst.)

Plasma—Cont'd
globulins in dog, effect of cortisone on, *90* (Abst.)
Platelet antibodies in allergy (Dameshek), 229
Platinum and related metals, contact dermatitis from, *83* (Abst.)
Plimasin, report of committee of Research Council of American Academy of Allergy on, 379
Pneumothorax, spontaneous, complicating asthma (Crepea) (Abst.), 88
Poliomyelitis and allergic constitution, *92* (Abst.)
Pollen crop, quality of (Dingle), 299
counts, atmospheric, in Toronto, Canada (Collins-Williams and Best), 461
extracts, fractionation of. II. Chemical and paper chromatographic investigation of ragweed pollen extracts (Frankel et al.), 33
timothy and low ragweed, highly concentrated, preparation of, by increasing concentration of extraction (Hampton et al.), 16
hay fever and asthma, treatment of, with aerosols of pollen extracts (Swineford and Lucas) (Abst.), 91
treatment with aerosols of pollen extracts (Swineford et al.), 305
injections, vaginal and urinary symptoms following, *65* (Abst.)
oils, tree, dermatitis venenata from (Lovell et al.), 408
predictions (Dingle), 300
survey of Northern California, 479 (Announcement)
Polyvinylpyrrolidone infusions, effect of, on immune response in rabbits, *89* (Abst.)
Posterior pituitary substances, anaphylactic reaction from (Keeney et al.), 144
Prantal, oral, in treatment of asthma and nasal allergies, *2* (Abst.)
Prednisone and prednisolone, major undesirable side-effects resulting from, *76* (Abst.)
in bronchial asthma (Schwartz), 206
in chronic asthma (Skaggs et al.), 201
in treatment of dermatoses, *70* (Abst.)
Pregnancy, cortisone and ACTH in, *16* (Abst.)
President's address, American Academy of Allergy, Feb. 7, 1955 (Sheldon), 275
Pressor drugs in inhalation therapy, safety of, *82* (Abst.)
Pressure breathing, intermittent positive, in inspiratory phase of respiration, *2* (Abst.)
Preventive medicine, allergist and, 75 (Editorial)
Primaquine, hemolytic effect of. II. Natural course of hemolytic anemia and mechanism of its self-limited character, *60* (Abst.)
Primaquine—Cont'd
III. Study of primaquine-sensitive erythrocytes, *61* (Abst.)
IV. Relation of cell age to hemolysis, *61* (Abst.)
Procaine amide in treatment and prevention of penicillin reactions, *72* (Abst.)
oral, in control of pruritus, *35* (Abst.)
penicillin, adverse reactions to, *57* (Abst.)
Pronestyl in treatment and prevention of penicillin reactions, *72* (Abst.)
Prophylaxis of summer hay fever and asthma, *18* (Abst.)
Protein antigens, immunologic unresponsiveness induced by, *77* (Abst.)
Proteins, analysis of, by electrophoresis and by Oudin's gel diffusion technique, *73* (Abst.)
Pruritus, oral procaine in control of, *35* (Abst.)
produced by zooea larvae of one of porcelain crabs, *22* (Abst.)
Psychiatric, pulmonary, and adrenocortical observations in bronchial asthma (Knapp and Michelson) (Abst.), 80
Psychosomatic study of positive skin reactions unrelated to bronchial asthma (Miller and Baruch), 54
Pulmonary disease, chronic, alveolar-arterial oxygen tension gradient in, evaluation of factors affecting, *64* (Abst.)
non-allergic, membrane changes in, significance of (Crepea and Harman), 453
function in asthmatic patients, effect of helium-oxygen mixtures on (Schiller et al.), 11
membranes, changes in, in asthmatic and non-allergic disease, significance of (Crepea and Harman), 453
psychiatric, and adrenocortical observations in bronchial asthma (Knapp and Michelson) (Abst.), 80
ventilatory function, studies in. I. Vital capacity, first one-second capacity, and forced respiratory curves in patients with asthma: comparative evaluation of methods (Roy et al.), 490
Pyribenzamine and Isuprel, aerosols of, pretreatment with, to prevent bronchial reactions to aerosols of specific haptens (Swineford et al.), 153
in treatment of nonhemolytic transfusion reactions, *91* (Abst.)
Pyridine radical, antihistaminic compounds containing, quantitative method for determination of, *75* (Abst.)

Q

Quantitative determination of histamine in animal tissues (McIntire), 292

R

Ragweed antigens, identification of, in gel diffusion precipitates, *49* (Abst.)
extermination campaign, New York City, effectiveness of (Walzer) (Abst.), 84
pollen extracts, chemical and paper chromatographic investigation of (Frankel et al.), 33
fractionation of (Perlman) (Abst.), 86
highly concentrated, preparation of, by increasing concentration of extraction (Hampton et al.), 16
preparation and preservation of, optimum concentration of glycerine in (Johnson et al.) (Abst., 89); 429
production of (Dingle), 299
Ragweed-sensitive patients, electrophoretic separation of skin-sensitizing antibody from (Rose et al.) (Abst.), 86
sera of, electrophoretic separation of skin-sensitizing antibody from (Sehon et al.), 329
Ratner, Bret, award to, 555 (Announcement)
Reaction, Löffler's to PAS, *73* (Abst.)
Shwartzman, fatal, during antibiotic therapy, *31* (Abst.)
Reactions, anaphylactic, caused by mixture of penicillin-streptomycin-procaine, *55* (Abst.)
severe, from oral penicillin, *25* (Abst.)
penicillin, in children (Matheson and Elegant), 415
procaine amide in treatment and prevention of, *72* (Abst.)
skin test, sensitization as applied to, studies in. III. Influence of age upon skin reactivity (Tuft et al.), 359
to benzathine penicillin, *58* (Abst.)
to iodides (Rasmussen), 395
to mercurial diuretics, *74* (Abst.)
to oxytetracycline hydrochloride, control studies of, *23* (Abst.)
to PAS, fatal allergic, *54* (Abst.)
to procaine penicillin in cats and man, *57* (Abst.)
to sodium dehydrocholate, *44* (Abst.)
toxic, to PAS and Isoniazid, *53* (Abst.)
tuberculin, of tuberculous patients on Isoniazid therapy, *56* (Abst.)
with drug therapy (Alexander), 383 (B. rev.)
Reagins exposed to beta-propiolactone, activity of human (Flick and Feinberg), 262
Red blood cells in allergy (Haberman), 219
Residencies in allergy, 556 (Announcement)
Respiration, effect on, of occlusion of bronchus in man during bronchospirometry, *46* (Abst.)
Respiration—Cont'd
inspiratory phase of, intermittent positive pressure breathing in, 2 (Abst.)
Respiratory allergies, childhood complications of (Harvard) (Abst.), 88
disease, chronic, role of Friedländer bacillus in, *19* (Abst.)
function in bronchial asthma, effect of corticotropin and cortisone on (Fyles et al.), 340
infections, citrus flavinoids in, *30* (Abst.)
response to carbon dioxide by salicylate, modification of, *92* (Abst.)
syndrome, smoker's, observations on, *3* (Abst.)
Reversed anaphylaxis in guinea pigs, effects of ACTH and cortisone on pathology of (Arbesman et al.), 123
Rheumatic fever, diphtheria antitoxin in, studies of, *47* (Abst.)
Rhinitis, allergic, cerebrospinal rhinorrhea simulating (Berryman), 71
intranasal corticotrophin in, *38* (Abst.)
nasal hydrocortisone in (Ogden et al.) (Abst.), 78
of pollen origin, treatment of, by use of suspension of Cortogen acetate with Chlor-Trimeton maleate, *34* (Abst.)
Rhus dermatitis, treatment of, with topical hydrocortisone, *67* (Abst.)
Roentgen irradiation, effect of, on capillaries, *90* (Abst.)
Rupture of esophagus, complication of status asthmaticus, *51* (Abst.)

S

Sandostene for treatment of allergic manifestations, *75* (Abst.)
Seasonal forecasts of pollen (Dingle), 300
Second International Congress on Allergology, 180 (Editorial)
Seitz type filter, new micro (Strauss and Spain), 471
Sensitivity, iodide, in etiology of periarteritis nodosa (Rasmussen) (Abst.), 81
of circulating eosinophils and capillary resistance to exogenous cortisone, *90* (Abst.)
reactions to iodides (Rasmussen), 395
sulfonamides to detect, *86* (Abst.)
tuberculin, in guinea pigs. influence of streptococcal toxin on development of, *40* (Abst.)
Sensitization as applied to skin test reactions, studies in. III. Influence of age upon skin reactivity (Tuft et al.), 359
dermal, duration of, following cellular transfer in guinea pigs (Chase and Battisto) (Abst.), 83
of human skin (Grolnick) (Abst., 83); 542
passive, of nitrogen mustard, effect on experimental production of arteritis by, *9* (Abst.)

Sensitization—Cont'd
penicillin, skin test in, value of (Matheson and Elegant), 415
studies in, as applied to skin testing procedures. II. Influence of allergen contact (Tuft and Heck), 59
Sensitizers, soap and detergents as, in hand dermatitis, *84* (Abst.)
Sensitizing antigen, acacia as (Silvette et al.), 509
properties of new drugs, experimental methods for detection of, shortcomings of (Mayer), 133
Serum, electrophoretic components of, relation of allergy reagins to, *15* (Abst.)
pattern in experimental hypersensitivity (Criep et al.) (Abst., 85); 519
glycoprotein concentrations following immunization in rabbit, *89* (Abst.)
neuritis, cortisone therapy in, dramatic response to, *86* (Abst.)
of rats immune to Nippostrongylus muris, absorption of protective antibodies from, *31* (Abst.)
sickness, acute pericarditis associated with, *8* (Abst.)
Shoes, dermatitis of feet due to, *69* (Abst.)
Shwartzman phenomenon in fatal infantile diarrhea, *78* (Abst.)
mechanism of, studies on, *75* (Abst.)
reaction during antibiotic therapy, *31* (Abst.)
localized, effect of Dicumarol on, *20* (Abst.)
Sinus disease, bacterial allergy and bronchial asthma (Siegal et al.) (Abst.), 80
Skin diseases, hydrocortisone acetate ointment in, *70* (Abst.)
human, sensitization of (Grolnick), 83 (Abst.)
lesions from insulin, nature and prevention of, *41* (Abst.)
reactions, positive, unrelated to bronchial asthma, psychosomatic study of (Miller and Baruch), 54
reactivity, influence of age upon (Tuft et al.), 359
sensitization of human (Grolnick), 542
sensitizing antibody, electrophoretic separation of, from ragweed-sensitive patients (Rose et al.) (Abst.), 86
from sera (Sehon et al.), 329
sensitivity test and modified antiglobulin test, comparison of, in Brucella infection in abattoir workers, *57* (Abst.)
test in penicillin sensitization, value of (Matheson and Elegant), 415
reactions, sensitization as applied to, studies in. III. Influence of age upon skin reactivity (Tuft et al.), 359
Skin diseases—Cont'd
response to multiple antigens, correlation of blood histamine release and (Noah and Brand), 385
testing methods in diagnosis of penicillin allergy, evaluation of (Tuft and Gregory) (Abst.), 92
procedures, studies in sensitization as applied to. II. Influence of allergen contact (Tuft and Heck), 59
tests to mold in Toronto, correlation of counts with (Collins-Williams and Best), 468
to pollens, correlations of counts with, in Toronto area (Collins-Williams and Best), 461
Smoker's respiratory syndrome, observations on, *3* (Abst.)
Soaps and detergents as primary irritants in hand dermatitis *85* (Abst.)
as sensitizers in hand dermatitis, *84* (Abst.)
Sociedad Mexicana de Alergistas, 479 (Announcement)
Sodium dehydrocholate, reactions to, *44* (Abst.)
Somatotrophic hormone and hydrocortisone acetate, influence of, on production of hemolytic antibodies in rat, *48* (Abst.)
Soybean diarrhea, folklore remedy for (Blue), 425
Sputum, asthmatic, chemical nature of, preliminary observations on (Bukantz and Schiele) (Abst.), 85
Status asthmaticus, blood volume in patients in, and during normal period (Lovell et al.) (Abst.), 90
rupture of esophagus complicating, *51* (Abst).
Stings, bee and wasp, allergic reactions to, *24* (Abst.)
Streptococcal toxin, influence of, on development of tuberculin sensitivity in guinea pigs, *40* (Abst.)
"Stresses" and hypersensitivity (Benaim et al.), 481
Sulfonamides, drug eruption from, *86* (Abst.)
Summer hay fever and asthma, prophylaxis of, *18* (Abst.)
Sweating, studies of. VI. On urticariogenic properties of human sweat, *3* (Abst.)
Symposium on role of formed elements of blood in allergy and hypersensitivity (Chase et al.), 219
Syphilis, secondary mucocutaneous, penicillin treatment of, in hypersensitive patient, use of cortisone during, *20* (Abst.)

T

Teldrin Spansule, treatment of allergic conditions with, *16* (Abst.)
Terramycin, reactions to, control studies of, *23* (Abst.)

Theophylline with ethylenediamine, effect of, on cerebral hemodynamics in presence of cardiac failure with and without Cheyne-Stokes respiration, *28* (Abst.)
Thromboembolic complications from cortisone therapy, *29* (Abst.)
Thyroid hormone level in blood, effect of epinephrine on, *11* (Abst.)
Timothy pollen extracts, highly concentrated, preparation of, by increasing concentration of extraction (Hampton et al.), 16
Transfusion reactions, allergic and pyrogenic antihistaminics for, *91* (Abst.)
nonhemolytic, antihistaminic drugs in treatment of, *91* (Abst.)
Tree pollen oils, dermatitis venenata from (Lovell et al.) (Abst., 89); 408
Trees, pollen counts of, in Toronto, Canada (Collins-Williams and Best), 464
Tributyrin, reaction to (Essellier et al.), 108
Triolein, reaction to (Essellier et al.), 108
Tripalmitin, reaction to (Essellier et al.), 108
Tromexan therapy, control of, *6* (Abst.)
Trypan blue, effect of compound 48/80 on localization of (Feinberg and Sternberger), 176
Tuberculin PPD and tuberculopolysaccharides, cutaneous reactivity to delayed and immediate, correlation between plasma, protein fractions, antibody titers and passive transfer of, *79* (Abst.)
fraction, purified, from unheated cultures in testing BCG-vaccinated subjects, *56* (Abst.)
reaction in skin windows in man, cytology of, *40* (Abst.)
nonspecific hyperergic reactivity at site of, studies on, *58* (Abst.)
of tuberculous patients on Isoniazid therapy, *56* (Abst.)
sensitivity in guinea pigs, influence of streptococcal toxin on development of, *40* (Abst.)
Tuberculins in BCG-vaccinated and unvaccinated persons, comparison of, *79* (Abst.)
international standard, PPD-S and Old Tuberculin, comparison between, *55* (Abst.)
Tuberculous rabbits, sera of, comparison of leukocyte lysis with certain immunologic phenomena in, *39* (Abst.)

U

Ulcerative colitis, ACTH and cortisone in treatment of, *30* (Abst.)
Undergraduate medical education in allergy (Sheldon's presidential address, American Academy of Allergy, Feb. 7, 1955), 275
Urinary and vaginal symptoms following pollen injections, *65* (Abst.)
corticoid excretion, effect of nonspecific therapy on (Rose et al.), 2
Urticaria and angioedema in children and young adults, *5* (Abst.)
subacute and chronic, low incidence of dermographism in, *36* (Abst.)
urinary corticoid excretion in (Rose et al.), 6

V

Vaginal and urinary symptoms following pollen injections, *65* (Abst.)
cream, Löffler's syndrome following use of, *24* (Abst.)
Vascular reactivity, effect of cortisone on, *63* (Abst.)
Vegetable oils, allergens in (Essellier et al.), 107
Vernal conjunctivitis, *71* (Abst.)
Vibazine, new antihistamine, clinical evaluation of (Gaillard), 373
Virus, non-infective, reactivation of, in cortisone-injected host, *78* (Abst.)
Vital capacity in asthma (Roy et al.), 490

W

Wasp and bee stings, allergic reactions to, *24* (Abst.)
Waterless hand cleaners, dermatitis from, *21* (Abst.)
"Wax" or acid-fast bacilli, sensitization of guinea pigs to *Micrococcus pyogenes var. aureus* in presence of, *59* (Abst.)
Weather and mold counts in Toronto, correlation between (Collins-Williams and Best), 470
pollen counts and, correlation between (Collins-Williams and Best), 462
role of, in hay fever problem (Dingle), 298
Weeds, pollen counts of, in Toronto, Canada (Collins-Williams and Best), 466
Wool, allergenic factor in atopic dermatitis, *35* (Abst.)

X

Xanthine compound, Parephyllin, cerebral hemodynamic response to, *29* (Abst.)
X-rays, effect of, on experimentally produced acute contact dermatitis, *69* (Abst.)

Z

Zooea larvae of one of porcelain crabs, pruritus produced by, *22* (Abst.)
Zoris, allergic eczematous contact-type dermatitis due to, *37* (Abst.)